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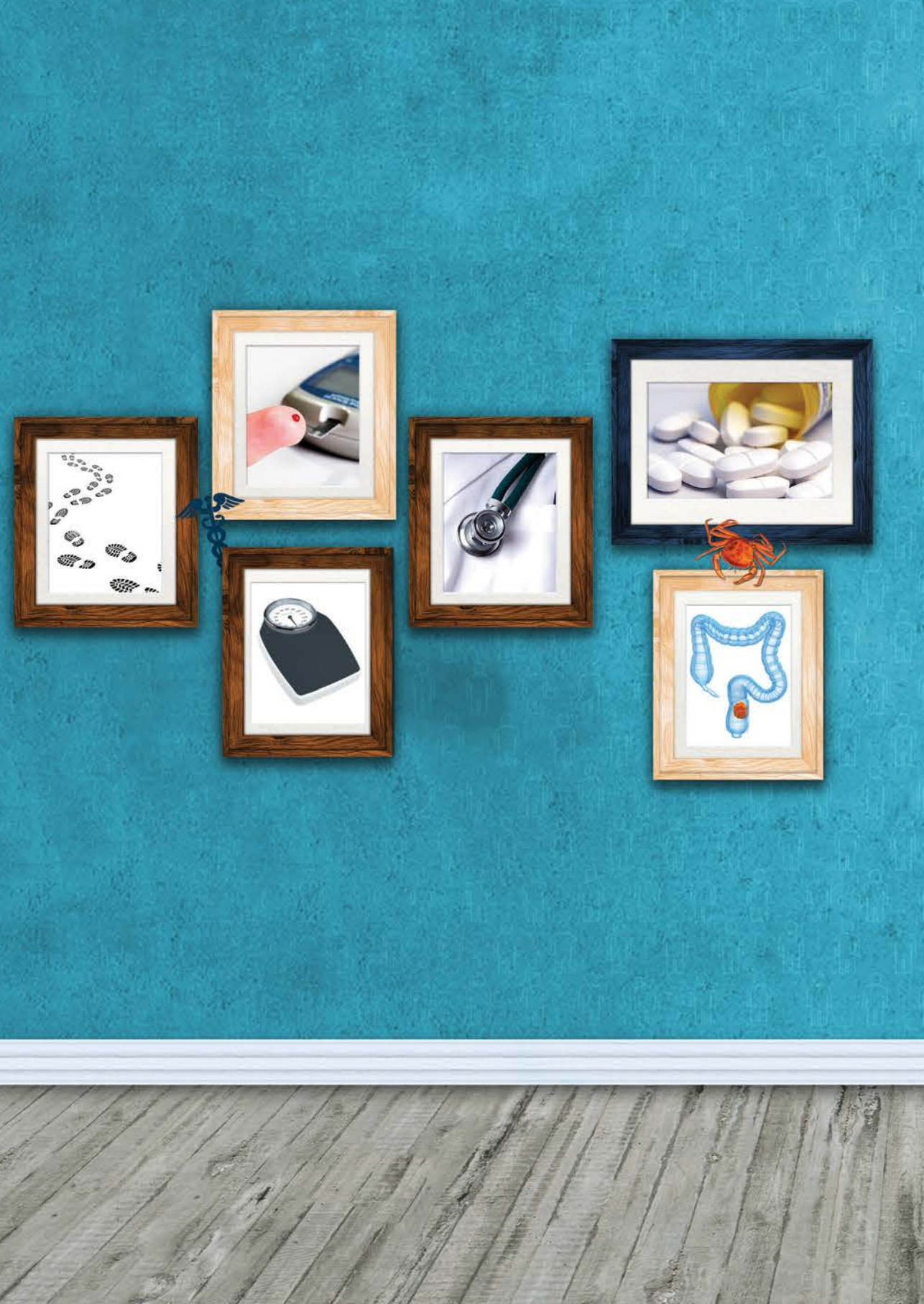

DIABETES AND CANCER – A DANGEROUS LIAISON?

The reciprocal impact of diabetes and cancer on outcomes with a special focus on drug effects

Marjolein Zanders

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General introduction, outline and data sources

General introduction

Cancer and type 2 diabetes are common diseases with a considerable impact on public health. Both diseases are complex and have multiple subtypes, while the underlying pathophysiology is not well understood. Individually, these diseases are the subject of study of many research groups worldwide.

Cancer is typically classified by its anatomic origin (of which there are hundreds) and within which there are multiple subtypes. In 2013, the most prevalent cancers in the Netherlands were prostate (21%), skin (basal cell carcinoma excluded; 14%) and colorectal cancer (CRC; 14%) among males and breast (30%), skin (basal cell carcinoma excluded; 14%) and CRC (12%) among females[1]. The various forms can behave very differently from one another, they can spread to different parts of the body through the bloodstream or lymphatic system (this is called metastasis), but the original site of the cancer cells determines the cancer type. Traditionally cancer is treated using surgery, radiotherapy and/or chemotherapy, but nowadays targeted therapies make personalised medicine a reality and will continue to help doctors tailor cancer treatment based on the characteristics of a tumour within an individual.

For adults with diabetes, type 2 diabetes is by far the most common type of diabetes (>90%) and is characterized by hyperglycaemia and variable degrees of insulin deficiency and resistance[2]. The majority of patients with type 2 diabetes, from now on referred to as diabetes, are asymptomatic and hyperglycaemia is noted on routine laboratory evaluation. Classic symptoms of hyperglycaemia, often noted only in retrospect, include polyuria, polydipsia, nocturia, blurred vision, and infrequently, weight loss[3]. The diagnosis is based on one of four abnormalities: a glycated haemoglobin ≥ 6.5% (HbA_{1c}; 48 mmol/mol), a fasting plasma glucose ≥ 7.0 mmol/L, a random elevated glucose with symptoms, or an abnormal oral glucose tolerance test (OGTT)[2,4]. After the diagnosis of diabetes, the glycaemic control is checked every three to six months by using the HbA_{1c} measurement and physicians try to achieve normal or near normal glycaemia with an HbA_{1c} goal of <7% (53 mmol/mol)[2,4]. Currently the Dutch guideline for the treatment of diabetes advises metformin, a biguanide, as first line treatment beside lifestyle advice as dietary modification, exercise and weight reduction[4,5]. However, when metformin fails to maintain normoglycaemia, additional agents are either added or substituted. Subsequent therapy can involve the use of up to 10 different drug families alone or in combination.

Morbidity from diabetes is a consequence of both macrovascular disease (coronary artery disease, peripheral arterial disease and stroke) and microvascular disease (retinopathy, nephropathy, and neuropathy)[2]. Once present, the progression of

these complications can be slowed with blood pressure lowering drugs, lipid-modifying agents (statins), laser therapy for advanced retinopathy and angiotensin-converting enzyme (ACE) inhibitors for nephropathy, beside the aggressive management of glycaemia with glucose lowering drugs (GLDs)[2].

Combined occurrence of diabetes and cancer

Diabetes and cancer are diagnosed within the same individual more frequently than would be expected by chance[6-8]. In 2009, the results of several studies were combined in a meta-analysis revealing that some cancers develop more commonly in patients with diabetes, while prostate cancer occurs less often in individuals with diabetes[8]. The highest cancer incidences in individuals with diabetes were found for cancers of the liver, pancreas and endometrium, while high incidences were seen for cancers of the colorectum, breast and bladder[8]. Consequently, a large proportion of cancer patients has diabetes, but this varies according to the type of cancer[9] (Table 1). This thesis mainly focussed on the association between diabetes and CRC, since CRC is one of the most prevalent cancer types and occurs in both male and female. Among female patients the prevalence of diabetes was also high for endometrial cancer patients. Research on the association between diabetes and endometrial cancer was subject of this thesis as well.

Burden of diabetes and cancer

With the ageing of the population, the more or less constant risk of developing cancer and the declining risk of dying from cancer, the number of cancer survivors has substantially increased. According to the presented numbers in the report 'Cancer in the Netherlands till 2020' the absolute 10-year prevalence will increase from 420,000 patients with cancer in 2009 till 660,000 patients with cancer in 2020[10]. In concordance with the prevalence of cancer, the prevalence of diabetes is increasing tremendously and strongly influenced by the ageing of population as well, since diabetes is mostly a disease of the elderly[11,12]. In addition, the increase in obesity and physical inactivity have an important role in the present rise of cancer and diabetes cases[13]. In the Netherlands in 2007 the number of individuals with diabetes was estimated to be 740,000 and in 2025 this is expected to increase to 1.3 million[11]. As a result of the dramatic increase in the number of patients with cancer or diabetes and the association between the diseases, in the Netherlands the number of newly diagnosed cancer patients who also have diabetes is expected to increase from about 5,500 per year in 2000 to 10,000 per year in 2015[10]. In 2010-2011 16% of the males and 13% of the females with cancer had diabetes at the time of cancer diagnosis in the area of the Eindhoven Cancer Registry (Table 1). An increasing number of medical specialists will be confronted with individuals suffering from both diseases.

Table 1. Prevalence of diabetes (%) among cancer patients at diagnosis.

Cancer type	Males			Females		
	1998-1999	2005-2006	2011-2012	1998-1999	2005-2006	2011-2012
Dutch population	12%	15%		10%	12%	
All types of cancer [a]	9%	13%	16% **	11%	13%	13% *
Pancreatic	18%	26%	26%	26%	28%	28%
Stomach	13%	13%	13%	14%	18%	20%
Liver	28%	39%	32%	18%	44%	14%
Oesophageal	11%	18%	17% *	15%	13%	12%
Colon	12%	15%	18% *	13%	16%	17% *
Rectal	8%	13%	16% *	13%	12%	15%
Lung	8%	14%	18% **	9%	13%	13% *
Kidney	6%	19%	19% *	16%	19%	16%
Breast				8%	9%	10% *
Cervical				9%	11%	7%
Endometrial				14%	18%	18%
Ovarian				9%	14%	12%
Prostate	8%	10%	13% **			
Testicular	0%	2%	3%			
Bladder	9%	14%	17% **	17%	13%	15%
Hodgkin lymphoma	4%	4%	8%	7%	5%	0%
Non-Hodgkin lymphoma	7%	11%	14% *	8%	14%	10%

[a] Except basal cell carcinoma; *P-trend<0.05; **P-trend<0.0001; Source: Eindhoven Cancer Registry and www.nivel.nl/incidentie-en-prevalentiecijfers-in-de-huisartsenpraktijk.

Potential mechanisms linking diabetes and cancer

The transformation towards a malignancy can be divided into different steps: the initiation, promotion (stimulation of cell growth) and progression of a tumour (invasion and metastasis). Diabetes has been hypothesised to be associated with cancer incidence and outcomes by affecting one or more steps of this pathway. It remains however unclear whether the association between diabetes and cancer is largely explained by shared risk factors (obesity, poor diet, physical inactivity, and aging), or whether diabetes itself, and the specific metabolic derangements typical of diabetes (i.e. hyperglycaemia, insulin resistance, and hyperinsulinaemia), increase the incidence and mortality risk of some types of cancer. Evidence is accumulating that hyperinsulinaemia promotes tumour cell growth directly via the insulin receptor or indirectly via the insulin-like growth factor I (IGF-1) receptor, which are expressed on many cancer cells[14]. The IGF-I receptor seems necessary for the transforming ability of several oncogenes[15], while insulin or the IGF-I can

stimulate the proliferation of tumour cells in vitro[16]. Moreover, mouse models showed that genetic manipulations that reduced IGF-1 signalling can lead to decreased tumour growth[17]. As a result, currently more than 100 clinical trials have examined the hypothesis that targeting the insulin and IGF-I receptor will be useful in cancer treatment.

Effect of diabetes on mortality among cancer patients

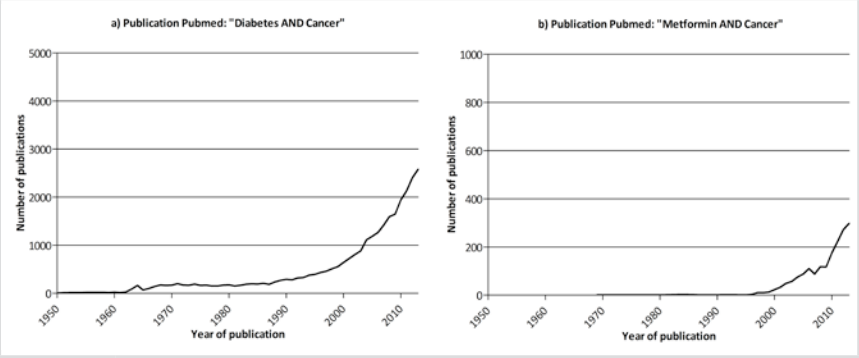
Uncertainty is great with respect to the association between diabetes and mortality among cancer patients. In 2010, as a result of these uncertainties, the American Diabetes Association and American Cancer Society reviewed the state of science concerning diabetes and cancer[6]. One of the key issues was a better understanding of whether diabetes influences cancer prognosis above and beyond the prognosis conferred by each disease state independently. Although several studies revealed that cancer patients with pre-existing diabetes had significantly worse overall mortality compared to patients without diabetes[9,18-25], the question remains if the combined effect of cancer and diabetes results in an even worse mortality than the sum of the individual effects of cancer and diabetes. As a result, there is a need for studies who address this question, dealing with differences in cancer treatment between patients with and without diabetes, adjusting for potential differences in patient and tumour characteristics and focussing on cancer outcomes, such as recurrence rates and cancer specific mortality. All of these factors might play a role in the association between diabetes and mortality in cancer patients and studies taking all, or at least most of them, into account are desired.

Since the pattern of cause of death is changing for diabetes patients – the risk of cardiovascular death in this group is declining – these patients might die of other causes, such as cancer. Thus in the near future, cancer might be the leading cause of death in individuals with diabetes. Therefore it is of utmost importance to further study the association between diabetes, cancer and mortality.

Current potential 'wonderdrugs' and their effect on mortality among cancer patients

In the past years, the number of papers on the association between diabetes and cancer increased tremendously[9,18,21,26] (Figure 1a). Furthermore, it was observed that the association between diabetes and mortality among cancer patients varied with GLDs, those treated with metformin appear to have decreased overall mortality[26-32] (Figure 1b). Most studies that investigated this association had incredibly low hazard ratios in favour of metformin, suggesting strong protective effects. However, they had important methodological limitations, since some analyses introduced immortal time bias and most analyses did not take into account the duration of drug use[27-32]. As a consequence of these limitations and the

Figure 1. a) Number of publications on Pubmed with search "Diabetes AND Cancer" per year; b) Number of publications on Pubmed with search "Metformin AND Cancer" per year.



potential of the used methods to induce or exaggerate protective effects, the debate on whether metformin might be a candidate drug as anti-tumour agent is ongoing[33].

Besides metformin, there are other current potential 'wonderdrugs', which seem to have an effect on mortality among cancer patients[34-41]. Two of these drug types, addressed in several groups of cancer patients are: statins, which are lipid modifying agents, and aspirin, which is an antithrombotic agent. They are frequently prescribed to individuals with diabetes, i.e. around 50% of the diabetes population use statins and 40% use aspirin according to the current international literature[42-44]. The high use of these drugs indicate that the use of metformin, statins and aspirin are strongly related and that their effect should be studied together while taking into account the use of each other drug. The current literature does not answer the justified question whether there is still an effect of metformin, statin and aspirin use on overall mortality if adjusted for one another.

The other perspective – the impact of cancer on diabetes control and drug use

The development of a tumour, the diagnosis of cancer and the treatment of cancer may all influence diabetes. The presence of cancer might result in worse glycaemic control and medication adherence, potentially resulting in more diabetes complications in individuals with diabetes and indirectly higher mortality. However, to our knowledge, till now these hypotheses are only speculations and not investigated properly.

HbA_{1c}, as a marker of glycaemic control, represents the average blood glucose level over the life span of a red blood cell, which is approximately three months[3].

The HbA_{1c}-value might be influenced directly by the tumour, the weight loss in cancer patients and/or the treatment of cancer, leading to (required or inappropriate) changes in medication. Moreover, according to a study on HbA_{1c} and mortality, individuals with diabetes and recent HbA_{1c} values < 6.5% (OR 1.3; 95% CI 1.2-1.4) and those with recent HbA_{1c} values > 9.0% (OR 1.5; 95% CI 1.3-1.7) had higher mortality compared to those with recent 'normal' HbA_{1c} values between 6.5% and 9%[45]. If the presence of cancer results in HbA_{1c}-values of < 6.5% or >9.0%, this will strengthen the hypothesis that the overall worse mortality seen in patients with diabetes and cancer might also be related to changes in glycaemic control due to cancer.
Good adherence to GLDs is crucial for achieving normal or near normal glycaemia (HbA_{1c} goal of <7%; 53 mmol/mol[2]) and prolonging survival time[46,47]. Overall, only 65%-85% of the users of GLDs is regarded as adherent[48,49]; this might decrease even more due to cancer. If the presence of a cancer diagnosis can influence medication adherence among users of GLDs, this could also affect HbA_{1c} levels leading to poor glycaemic control, higher risk of diabetes complications and worse overall mortality.

Outline

The research underlying this thesis aimed to understand how the combined effect of cancer and diabetes results in a worse mortality than the sum of the individual effects of cancer and diabetes.
The main objectives of the studies described in this thesis were (Figure 2):

- To assess the impact of diabetes on cancer treatment, cancer recurrence, cancer-specific and overall mortality in cancer patients.
- To assess whether, and to which extent, metformin, statin and aspirin use is associated with overall mortality in CRC patients with diabetes.
- To explore changes in glycaemic control and medication adherence among individuals with diabetes at the time of cancer diagnosis.

As an introduction to this thesis we evaluated and summarised the epidemiological evidence available on the magnitude of the deteriorated outcomes among patients who have both diabetes and CRC and reviewed potential variables and pathways associated with worse outcome (**Part I; Chapter 2**).

In **Part II** of this thesis the impact of diabetes on the administration of cancer treatment, cancer recurrence and cancer-specific and overall mortality was evaluated. To assess the reciprocal impact of diabetes and cancer on mortality extensively, a study among endometrial cancer (EC) patients was performed. The influence of diabetes on cancer stage at diagnosis, cancer recurrence, and survival

was investigated, while the influence of the treatment of EC on glycaemic control, GLDs use, and complications of diabetes was investigated as well (**Chapter 3**). As CRC patients with diabetes have worse survival rates compared with those without diabetes, it is hypothesized to be at least partly explained by less aggressive cancer treatment for individuals with diabetes. In this thesis we described differences in patient, tumour, and treatment related variables between CRC patients with and without diabetes, thereby evaluating the implementation of national treatment guidelines (**Chapter 4**). The effect of diabetes on the administration of cancer treatment was assessed separately for colon and rectal cancer patients, because these types of cancer are treated differently.

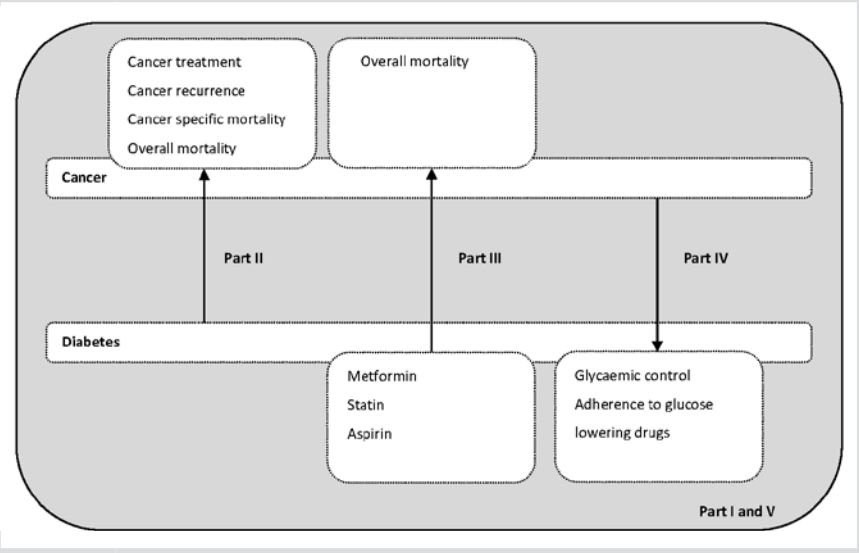
At the start of the research for this thesis numerous studies showed that the association between diabetes, cancer and mortality seemed to vary with GLDs, those treated with metformin appeared to have decreased overall mortality. These studies aroused our interest in metformin (**Part III**). The association between metformin use started after CRC diagnosis and mortality was explored using complex pharmaco-epidemiological analyses (**Chapter 5**). In the context of these complex analyses, this thesis includes a correspondence to the editor of the Journal of Clinical Oncology related to a study on metformin, mortality and prostate cancer (**Chapter 6**). Methodological considerations in the study of Margel et al. are discussed that are relevant in part III of this thesis.
Since the use of metformin, statin and aspirin, individually have been associated with decreased mortality in cancer patients and almost all individuals with diabetes receive statins and aspirins as co-medication, we assessed whether these drugs independently of one another influenced overall mortality in CRC patients (**Chapter 7**).

Many studies provide insight into the influence of diabetes and GLDs on outcomes after cancer diagnosis. However, the worse mortality observed among patients with both diabetes and cancer can also be the result of the influence of cancer on diabetes parameters and GLDs. We aimed to reduce this gap in the literature by the addition of the studies in **Part IV**.
Since no information is available about the impact of cancer on glycaemic control and physicians hypothesize that cancer deteriorates glycaemic control, which potentially influences mortality, we evaluated changes in HbA_{1c} values around CRC diagnosis (**Chapter 8**). Furthermore, we were interested if the adherence to GLDs changes due to cancer diagnosis and treatment in individuals with diabetes, because worse medication adherence might lead to a higher risk of diabetes

complications and mortality (**Chapter 9**).

In the general discussion the main findings and methodological considerations are discussed and implications for future research and clinical practice are outlined (**Part V**; **Chapter 10**).

Figure 2. Research questions investigated in this thesis.



Data sources

Eindhoven Cancer Registry

The Eindhoven Cancer Registry (ECR) started in 1955 as part of a programme for nationwide cancer registration. Data on all newly diagnosed cancer patients were collected directly from pathology reports and medical records, sometimes through emerging hospital discharge registries. The registry started in three hospitals in Eindhoven and gradually expanded to include the southeastern part of the province of Noord-Brabant, the northern part of the province of Limburg (since 1970) and the middle and southwestern part of Noord-Brabant since 1986 (Figure 3).

Figure 3. The area of the Eindhoven Cancer Registry of the Netherlands Comprehensive Cancer Organisation.

The area in the population-based ECR now hosts 2.4 million inhabitants and is served by 10 community hospitals, 6 regional pathology laboratories all participating in the nationwide network and registry of histo- and cytopathology (PALGA) and two large radiotherapy departments. The region is characterised by good access to medical care without financial obstacles. The distance to a hospital has always been less than 30 kilometres.

Trained registration clerks actively collect data on diagnosis, patient characteristics,

staging, and detailed information about initial treatment (delivered within 6 months from diagnosis) from hospital medical records. The medical record is generally regarded as the most complete source of information on the patient's past and current health status. Information on the vital status of the patients is obtained from the nationwide municipal personal records database. Since these registries do not provide information about the cause of death, additional data collection for information on cause of death was performed for one study in this thesis.

Comorbidity at cancer diagnosis is obtained from the medical records by registration clerks and registered in the ECR according to an adapted version of the Charlson Comorbidity Index since 1993[50]. Comorbidity was defined as life-shortening diseases that were present at the time of cancer diagnosis. The use of medication serves as an indicator for active disease, but comorbidity is only registered when it is described in the medical record. Diabetes includes both type 1 and type 2 diseases and is registered as a dichotomous variable (yes/no), as are all other concomitant conditions.

PHARMO Database Network

The PHARmacoMOrbidity (PHARMO) Database Network is a population-based network of healthcare databases and combines data from different healthcare settings in the Netherlands. These different data sources are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere[51,52]. The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. Since the data collection period, catchment area and overlap between data sources differs, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality, while other information available is dependent on the data source. A detailed description of the different data sources is given below.

For this thesis the Out-patient Pharmacy Database comprises general practitioner or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, and quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System[53]. The out-patient pharmacy

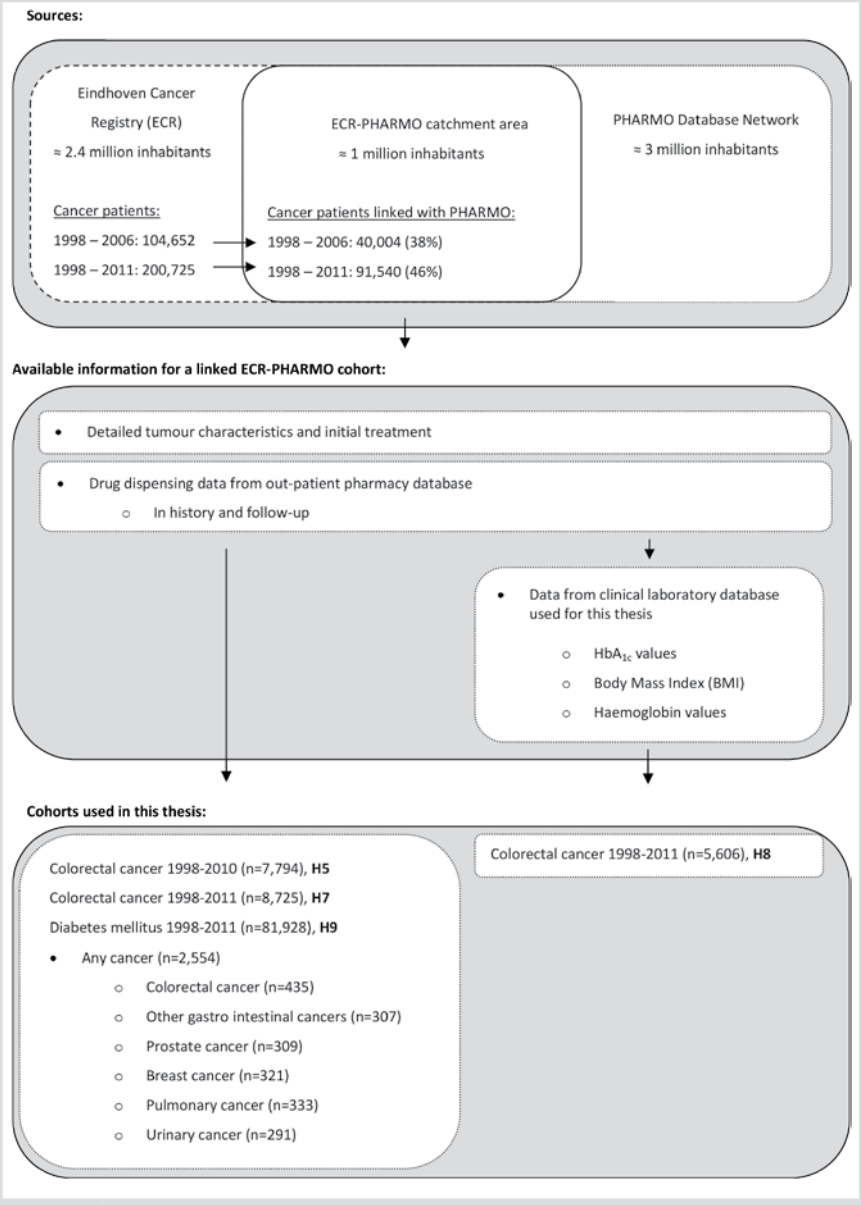
data cover a catchment area representing 3.6 million residents.

The Clinical Laboratory Database comprises results of tests performed on clinical specimens. These laboratory tests are requested by general practitioners and medical specialists in order to get information concerning diagnosis, treatment, and prevention of disease. The electronic records include information on date and time of testing, test result, unit of measurement and type of clinical specimen. Laboratory tests are coded according to the Dutch WCIA coding system[54]. The clinical laboratory data cover a catchment area representing 1.2 million residents.

Linkage of ECR with PHARMO

Both the ECR and the PHARMO Database Network are recognised as high quality sources for epidemiological research that collect information in overlapping regions in the Netherlands for a period of at least 10 years[52]. For this thesis data were obtained from the ECR and linked on a patient level to the PHARMO Database Network, covering a demographic region in the southeastern part of the Netherlands of approximately one million inhabitants. The construct and validity of the ECR-PHARMO cohort have been described in detail elsewhere[52].
The first cohort obtained after the linkage of the ECR and PHARMO databases consisted of 40,004 patients diagnosed with cancer between 1998 and 2006, 38% of the 104,562 cancer patients within the ECR were successfully linked (Figure 4)[52]. After the inclusion of five more years of cancer patients (1998 – 2011), the size of the linked ECR-PHARMO cohort more than doubled to 91,540 patients. As a result of the expansion of the PHARMO Database Network within the ECR region, the percentage of cancer patients linked with PHARMO increased from 38% to 46% (Figure 4). For this thesis specific groups of cancer patients from the linked ECR-PHARMO cohort were selected to answer the research questions, as can be seen in Figure 4.

Figure 4 Flowchart of the linkage process and cohort formation for this thesis.



References

1. www.cijfersoverkanker.nl, Source Comprehensive Cancer Centre the Netherlands (IKNL), Accessed 07-07-2014.
2. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1:S62-9.
4. Bouma M, Rutten GE, de Grauw WJ, Wiersma T, Goudswaard AN. [Summary of the practice guideline 'Diabetes mellitus type 2' (second revision) from the Dutch College of General Practitioners]. Ned Tijdschr Geneeskd. 2006;150(41):2251-6.
5. Wiersma TJ, Heine RJ, Rutten GE. [Summary of the practice guideline 'Diabetes mellitus type 2' (first revision) of the Dutch College of General Practitioners]. Ned Tijdschr Geneeskd. 1999;143(33):1688-91.
6. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.
7. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55(6):1607-18.
8. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009;16(4):1103-23.
9. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
10. Cancer in the Netherlands till 2020 (2011) Trends and prognoses. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-00-8.
11. Baan CA, van Baal PH, Jacobs-van der Bruggen MA, Verkley H, Poos MJ, Hoogenveen RT, et al. [Diabetes mellitus in the Netherlands: estimate of the current disease burden and prognosis for 2025]. Ned Tijdschr Geneeskd. 2009;153(22):1052-8.
12. Sloan FA, Bethel MA, Ruiz D, Shea AM, Feinglos MN. The growing burden of diabetes mellitus in the US elderly population. Arch Intern Med. 2008;168(2):192-9; discussion 9.
13. Imes CC, Burke LE. The Obesity Epidemic: The United States as a Cautionary Tale for the Rest of the World. Curr Epidemiol Rep. 2014;1(2):82-8.
14. Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. Nat Rev Cancer. 2012;12(3):159-69.
15. Sell C, Rubini M, Rubin R, Liu JP, Efstratiadis A, Baserga R. Simian virus 40 large tumor antigen is unable to transform mouse embryonic fibroblasts lacking type 1 insulin-like growth factor receptor. Proc Natl Acad Sci U S A. 1993;90(23):11217-21.
16. Osborne CK, Bolan G, Monaco ME, Lippman ME. Hormone responsive human breast cancer in long-term tissue culture: effect of insulin. Proc Natl Acad Sci U S A. 1976;73(12):4536-40.
17. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer. 2008;8(12):915-28.
18. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754-64.
19. Jullumstro E, Kollind M, Lydersen S, Edna TH. Diabetes mellitus and outcomes of colorectal cancer. Acta Oncol. 2009;48(3):361-7.
20. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, 3rd, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003;21(3):433-40.
21. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol. 2011;30(1):53-9.
22. Stein KB, Snyder CF, Barone BB, Yeh HC, Peairs KS, Derr RL, et al. Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: a systematic review and meta-analysis. Dig Dis Sci. 2010;55(7):1839-51.
23. van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. Diabetologia. 2012;55(8):2163-72.

24. Bella F, Minicozzi P, Giacomin A, Crocetti E, Federico M, Ponz de Leon M, et al. Impact of diabetes on overall and cancer-specific mortality in colorectal cancer patients. J Cancer Res Clin Oncol. 2013;139(8):1303-10.

25. Polednak AP. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: a population-based study. Cancer Detect Prev. 2006;30(5):466-72.

26. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-32.

27. Garrett CR, Hassabo HM, Bhadkamkar NA, Wen S, Baladandayuthapani V, Kee BK, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012;106(8):1374-8.

28. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care. 2010;33(2):322-6.

29. Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer. 2011;131(3):752-9.

30. Cossor FI, Adams-Campbell LL, Chlebowski RT, Gunter MJ, Johnson K, Martell RE, et al. Diabetes, metformin use, and colorectal cancer survival in postmenopausal women. Cancer Epidemiol. 2013;37(5):742-9.

31. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299-304.

32. Spillane S, Bennett K, Sharp L, Barron TI. A cohort study of metformin exposure and survival in patients with stage I-III colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2013;22(8):1364-73.

33. Suissa S, Azoulay L. Metformin and cancer: mounting evidence against an association. Diabetes Care. 2014;37(7):1786-8.

34. Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. Gut. 2010;59(11):1572-85.

35. Lakha F, Theodoratou E, Farrington SM, Tenesa A, Cetnarskyj R, Din FV, et al. Statin use and association with colorectal cancer survival and risk: case control study with prescription data linkage. BMC Cancer. 2012;12:487.

36. Siddiqui AA, Nazario H, Mahgoub A, Patel M, Cipher D, Spechler SJ. For patients with colorectal cancer, the long-term use of statins is associated with better clinical outcomes. Dig Dis Sci. 2009;54(6):1307-11.

37. Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJ, van Herk-Sukel MP, Lemmens V, et al. Use of aspirin postdiagnosis improves survival for colon cancer patients. Br J Cancer. 2012;106(9):1564-70.

38. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 2009;302(6):649-58.

39. Walker AJ, Grainge MJ, Card TR. Aspirin and other non-steroidal anti-inflammatory drug use and colorectal cancer survival: a cohort study. Br J Cancer. 2012;107(9):1602-7.

40. McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. Eur J Cancer. 2013;49(5):1049-57.

41. Ganz PA, Habel LA, Weltzien EK, Caan BJ, Cole SW. Examining the influence of beta blockers and ACE inhibitors on the risk for breast cancer recurrence: results from the LACE cohort. Breast Cancer Res Treat. 2011;129(2):549-56.

42. Ekstrom N, Cederholm J, Zethelius B, Eliasson B, Fharm E, Rolandsson O, et al. Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register. BMJ Open. 2013;3(4).

43. Smiechowski B, Azoulay L, Yin H, Pollak MN, Suissa S. The use of metformin and colorectal cancer incidence in patients with type II diabetes mellitus. Cancer Epidemiol Biomarkers Prev. 2013;22(10):1877-83.

44. van Dijk L, Wolters I, de Bakker DH. NIVEL: Farmaceutische zorg in de integrale bekostiging, http://www.nivel.nl/sites/default/files/bestanden/Rapport-Farmaceutische-zorg-in-tegrale-bekostiging.pdf. 2011.

45. Nicholas J, Charlton J, Dregan A, Gulliford MC. Recent HbA_{1c} values and mortality risk in type 2 diabetes. population-based case-control study. PLoS One. 2013;8(7):e68008.

46. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal effects of medication nonadherence on glycemic control. Ann Pharmacother. 2014;48(5):562-70.

47. Lawrence DB, Ragucci KR, Long LB, Parris BS, Helfer LA. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. J Manag Care Pharm. 2006;12(6):466-71.

48. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. Clin Med Res. 2013;11(2):54-65.

49. Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. Am J Med. 2005;118 Suppl 5A:27S-34S.

50. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

51. Herings RMC, Pedersen L. Pharmacy-based Medical Record Linkage Systems. In: Strom BL, Kimmel SE, Hennessy S, editors. Pharmacoepidemiology, 5th Edition. John Wiley & Sons, Ltd; 2012. p. 270-86.

52. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395-404.

53. World Health Organization. Collaborating Centre for Drug Statistics Methodology - ATC/DDD index. Accessed at www.whocc.no/atc_ddd_index, 2014.

54. http://www.nhgonline.nl/viewers/labcodeviewer/

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Colorectal cancer, diabetes and survival: epidemiological insights

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Abstract

Colorectal cancer (CRC) patients with pre-existing diabetes have significantly lower rates of overall survival compared with patients without diabetes. Against this backdrop, the American Diabetes Association and American Cancer Society in 2010 reviewed the scientific literature concerning diabetes and cancer. One of the key issues identified for further investigation was the need for a better understanding of whether diabetes influences cancer prognosis above and beyond the prognosis conferred by each disease state independently. Whether the worsened survival of CRC patients with diabetes could be explained by less favourable patient-, tumour- and treatment related characteristics has also been elevated in numerous recent studies. However, as most studies did not account for all the various potential confounders, such as cancer stage, comorbidities and body mass index (BMI) in their analyses, the current evidence for the association between diabetes and survival in CRC patients remains inconclusive. Nevertheless, based on multiple examples in the literature, the present review demonstrates that diabetes affects the presentation of CRC as well as its treatment and outcome, which may then result in lower overall rates of survival in patients with, compared to those without, diabetes.

Introduction

Colorectal cancer (CRC) is more common in people with diabetes than in those without diabetes[1-4], and patients with diabetes also have lower overall survival rates after CRC compared to those without diabetes, with 5-year survival of 35% and 48%, respectively[5-13]. In this context, the American Diabetes Association and American Cancer Society in 2010 reviewed the scientific literature concerning diabetes and cancer. One of the key issues identified for further investigation was the need for a better understanding of whether diabetes influences cancer prognosis above and beyond the prognosis conferred by each disease on its own[14]. This increased focus on diabetes, cancer and mortality has led to a rapid increase in reported observational studies using various data sources[5-13] and the finding that the presence of diabetes can lead to lower overall survival in CRC patients by affecting the diagnosis, treatment and other outcomes of CRC. However, the association between diabetes and survival in CRC patients is highly complex, and many underlying factors, both known and unknown, could play a role. The aim of the present review was to evaluate and summarize the epidemiological evidence available on the magnitude of outcome worsening among patients who have both diseases, and to review the potential variables and pathways associated with those poorer outcomes.

To this end, a comprehensive literature review was used to examine the differences due to various factors associated with CRC in patients with and without diabetes that might be contributing to the higher mortality in those with diabetes. The associations explored are presented in Figure 1.

Worsened outcomes among patients with colorectal cancer and diabetes

Overall survival

In several studies, cancer patients with pre-existing diabetes had significantly poorer overall survival compared to patients without diabetes[5-13] (Table 1). When considering colon and rectal cancer separately, diabetes was significantly associated with lower overall survival in colon cancer patients, whereas this was less clear for rectal cancer patients[7,9,12,15-17]. One study showed that diabetes was associated with overall survival in patients with proximal colon cancer, but not in patients with distal colon cancer[15]. These cancer site-specific findings imply that diabetes not only influences the survival in CRC patients through shared risk factors, but may also influence the various subsites differently by affecting tumour and treatment characteristics (see below; Figure 1).

Table 1. Studies looking at the relationship between diabetes and mortality in colorectal cancer patients.

Authors, year	Cancer type	Study design (No. of studies)	Diabetes patients (n)	Overall mortality HR (95% CI) [a]	CRC-specific mortality HR (95% CI) [a]
Meyerhardt et al., 2003[8]	Colon (stage II/III)	Cohort	287	1.42 (1.22-1.67)	
Larsson et al., 2005[3]	Colorectal	Meta-analysis (6)	138,728		1.26 (1.05-1.50)
Polednak et al., 2006[12]	Colorectal	Population based	1014	1.38 (1.27-1.49)	1.06 (0.94-1.20)
Van de Poll-Franse et al., 2007[13]	Colon	Population-based	422	1.28 (1.14-1.42)	
	Rectal	Population-based	217	1.48 (1.28-1.73)	
Barone et al., 2008[5]	Colorectal	Meta-analysis (6)	54,740	1.32 (1.24-1.41)	
Jullumstro et al., 2009[7]	Colorectal	Cohort	97	1.36 (1.07-1.72)	
Stein et al., 2010[9]	Colorectal	Meta-analysis (6)	8,984	1.32 (1.24-1.41)	
Dehal et al., 2011[11]	Colorectal	Cohort	393	1.53 (1.28-1.83)	1.29 (0.98-1.70)
Huang et al., 2011[16]	Colon	Cohort	469	1.21 (1.04-1.41)	1.21 (1.02-1.43)
Jiang et al., 201[11]	Colorectal	Meta-analysis (11)	Not stated		1.25 (1.08-1.44)
Van Waalwijk et al., 2011[17]	Colon	Cohort	201	0.99 (0.74-1.32)	
Van de Poll-Franse et al., 2012[10]	Colon	Population-based	820	1.12 (1.01-1.25)	1.05 (0.90-1.23)
	Rectal	Population-based	404	1.21 (1.03-1.41)	1.30 (1.06-1.60)
Bella et al., 2013[6]	Colorectal	Population-based	373	1.41 (1.18-1.70)	1.36 (1.11-1.67)
	Colon	Population-based	253	1.26 (1.01-1.57)	1.21 (0.94-1.55)
	Rectal	Population-based	120	1.89 (1.34-2.68)	1.70 (1.08-2.67)
Jeon et al., 2013[15]	Colon	Cohort	288	1.46 (1.11-1.92)	1.25 (0.87-1.80)
	Rectal	Cohort	229	0.96 (0.73-1.27)	0.92 (0.65-1.31)

[a] Hazard ratios for patients with vs. without diabetes (reference group).

Cancer-specific survival

Although the attention on cancer-specific survival is increasing (Table 1), studies show mixed results and experts in cancer epidemiology recognize that the attribution of cause of death is often problematic[18-20]. Cause of death information taken from death certificates is frequently inaccurate and incomplete[21]. In addition, unreliable cause of death information can lead to misleading results[22]. This was well demonstrated by a previous study of CRC-specific survival in which 34% of rectal cancer patients were registered as having colon cancer as their underlying cause of death[9]. A few studies on CRC-specific survival found that diabetes was associated with lower rates of survival[1,10,13], although others observed significantly worse CRC-specific survival only with rectal cancer[9,13] (Table 1). More consistent was the finding that, when comparing CRC patients with and without diabetes, an increased risk of death due to other causes, especially cardiovascular disease, was evident[9-11]. However, in many of the above-mentioned studies, the analyses did not consider the presence of competing risks, i.e. the risk of death due to cancer competing with the risk of death due to other causes, especially cardiovascular disease[18-20]. As CRC patients with diabetes have a greater risk of dying from a cardiovascular event than cancer patients without diabetes, Cox regression analysis may have overestimated the actual risk of cancer death in diabetes patients[19,20]. To obtain a comprehensive picture of the impact of diabetes on survival, other causes of death must not be ignored, and overall survival analyses should be included as a point of reference. In addition, given the presence of competing risks, a cause-specific hazards model which combines proportional hazards models for the event of interest and the competing event may be more appropriate[20].

Cancer recurrence

One study evaluated the impact of diabetes on CRC recurrence and reported that patients with diabetes experienced a 5-year recurrence-free survival rate of 56% compared to 64% for those without diabetes[7]. Moreover, during the study follow-up, those with diabetes were more likely to die of recurrent disease[7]. Another study showed that the risk of recurrence was 32% higher in colon cancer patients with compared to those without diabetes, although this was not statistically significant[15]. One explanation for the apparently higher recurrence rates in CRC patients with compared to without diabetes could be increase tumour cell proliferation and metastases in the physiological environment of hyperinsulinaemia and hyperglycaemia[23]. As a consequence, the association between diabetes and cancer recurrence might be important in the overall relationship between diabetes and survival in CRC patients. In this case, additional studies focussing on cancer recurrence are needed.

Conclusions

There is extensive evidence that diabetes is associated with lower overall survival in CRC patients, although the data for cancer-specific survival and cancer recurrence are currently limited in the literature. Future studies need to bear in mind that the attribution of cause of death is often problematic and that the presence of competing risks should also be considered.

Common risk factors

The association between diabetes and prognosis in CRC patients is highly complex, as many underlying risk factors, such as age, lifestyle factors and comorbidities may be associated with the risk of diabetes and CRC as well as the prognosis after CRC[14,24] (Figure 1).

Age

A strong well-known prognostic factor in general is age, and the finding that CRC patients with diabetes are on average 3 to 5 years older than those without diabetes may have a major influence on the difference in mortality between the two groups[6,9,15]. Having a combination of both diseases is more common in the elderly, as the incidence of colon and/or rectal cancer is highest in those aged ≥65 years, while the peak incidence of diabetes is at an even older age, around 76 years in the Netherlands[9,25-27].

Lifestyle

Lifestyle factors, such as unhealthy diet, obesity and physical inactivity can influence the prognosis following CRC either directly or indirectly, as these factors may promote the development of other conditions, such as diabetes and cardiovascular disease[28]. Smoking is one such factor, as it may influence prognosis directly via the development of lung and cardiovascular disease, or indirectly in those with diabetes[29]. Among diabetes patients, smoking substantially raises the risk of neuropathy and nephropathy, resulting in a poorer prognosis for patients with both CRC and diabetes[29]. In addition, greater adherence to a typical Western diet (characterized by higher intakes of meat, sweets and refined grains) has been associated with significantly lower disease-free survival after a diagnosis of colon cancer[30,31].

Physical inactivity and obesity are potentially important confounding factors that should be considered, as both are hypothesized to influence insulin resistance and hyperinsulinaemia, thereby, indirectly affecting cancer outcomes[32]. Lack of exercise and being overweight are both strongly associated with the incidence of type 2 diabetes, with more severe obesity being linked directly to diabetes

onset at an earlier age[33,34]. In one study in CRC patients, those with obesity before cancer diagnosis had lower rates of survival compared to those of normal weight and the association appeared to be stronger for patients diagnosed with rectal, rather than colon, cancer[35]. Although this poorer survival in obese patients may be related to suboptimal surgical resection, one study of laparoscopic surgery for rectal cancer showed that body mass index (BMI) influenced the risk of conversion to an open procedure, but not surgical morbidity, quality of surgery or survival[36]. A meta-analysis of prospective cohort studies indicated that physical activity both before and after cancer diagnosis was associated with less CRC-specific mortality and overall mortality[37,38]. However, as BMI and physical activity can change over time, particularly during CRC therapy, repeated measurements of these lifestyle factors are likely to reduce misclassifications over time and so better reflect the effects of these factors on cancer survival[39]. Indeed, this was demonstrated by a longitudinal study in which BMI and physical activity in CRC patients were followed over time[39]. The CRC patients who were underweight at the time of diagnosis had worse cancer-specific survival, whereas patients who were either physically active or overweight had better cancer-specific survival. At 5 months post-diagnosis, CRC patients who had either lost or gained weight had lower overall survival, whereas those who increased their physical activity had higher survival rates[39].

Comorbidities

The association between various comorbidities and mortality was demonstrated decades ago[40]. Among CRC patients, those with diabetes have a significantly greater prevalence of cardiovascular disease, hypertension and cerebrovascular disease compared to those without diabetes, with prevalent rates of nearly 50%[9,12,27]. In addition, diseases of the circulatory system are more often registered as the underlying cause of death in CRC patients with vs. those without diabetes, with rates of 18% vs. 12%, respectively[9]. Furthermore, besides vascular comorbidities, CRC patients with diabetes have more often been diagnosed with previous cancer and lung disease than those without diabetes[9]. However, although comorbidities appear to have led to the lower overall survival in patients with diabetes, the poorer cancer-specific survival found in some studies could not be explained by the high prevalence of comorbidities[9,13,16].

Conclusions

Age, smoking, dietary habits, BMI, physical activity and comorbidities are important potential confounding factors that should be considered when investigating the relationship between diabetes and overall mortality as well as cancer-specific mortality in CRC patients.

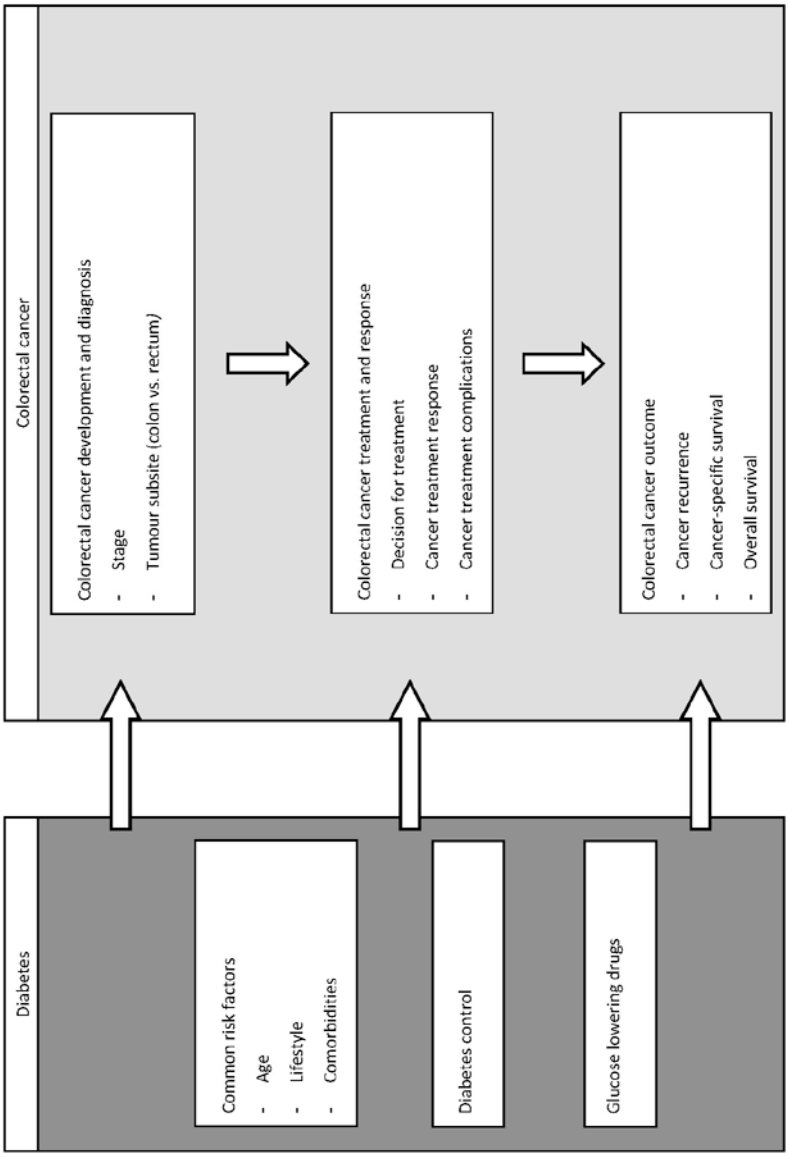

Figure 1. Schematic model of the relationship between diabetes and survival in colorectal cancer (CRC) patients.

Colorectal cancer development and diagnosis

Cancer stage

The most important prognostic factor in both colon and rectal cancer patients is the stage of the tumour at the time of diagnosis, with survival decreasing with increasing stage. Thus, if diabetes affects cancer stage at diagnosis, then, diabetes may have a major impact on survival among CRC patients. One study found that diabetes was associated with a trend towards diagnosis of early-stage (vs. late stage) CRC[41], while another study found that poorly controlled diabetes, defined as an HbA_{1c} value ≥7.5%, was particularly associated with a later stage of cancer at diagnosis[42]. It may be that, in such patients, medical care is focused on the management of diabetes and complications related to high blood glucose rather than on symptoms suggestive of cancer[43]. However, other studies support the theory (proposed by Feinstein) that earlier-stage disease is found in those with comorbidities because of increased contact with healthcare providers[41,42,44,45]. Indeed, extensive investigation of a newly diagnosed patient with diabetes increases the chances of detecting early-stage cancer[46]. Recent observational studies addressing the time-varying risk of cancer incidence following diabetes onset have suggested that a substantial degree of detection bias in patients with diabetes is most likely due to increased ascertainment leading to earlier detection[46] (Figure 1). This detection bias in those with diabetes may indirectly influence the prognosis of patients with CRC, as those with early-stage CRC have better chances of curative treatment.

Tumour subsite (colon vs. rectum)

Within the CRC patient population, differences in mortality are observed across various subsites. While the survival of patients with rectal cancer was worse than those with colon cancer in the years up to 2000, changes in the management of rectal cancer have since led to its survival rates levelling with those for colon cancer[47]. Although one study found that diabetes was associated with a risk of proximal colon cancer[48] and not distal colon or rectal cancer, another study found that diabetes was associated with risk at all subsites[49]. In view of the difference in treatment regimens for colon and rectal cancer as well as the effect of diabetes on survival, colon and rectal cancer should be analyzed separately[9,12,13,15]. According to tumour subsites, the evidence for survival in CRC patients with diabetes is inconclusive; some studies have shown poorer CRC-specific survival for rectal cancer patients with diabetes, but not for colon cancer patients with diabetes[9,13], while a study of colon cancer patients showed lower CRC-specific survival[16]. In addition, distal colon tumours have been associated with a decreased CRC-specific mortality compared to proximal colon tumours[50]. Thus, further studies of CRC-specific survival in these subgroups are needed, including a large-scale

population study taking into account the presence of competing risks, as discussed above.

Conclusions

Evidence for the association between diabetes and stage of CRC at diagnosis is conflicting, with findings for both earlier as well as more advanced stages in patients with diabetes. Given the mixed results of previous research, the relationship between diabetes and survival in colon and rectal cancer patients should be addressed separately.

Colorectal cancer treatment and response

Decision for treatment

The lower overall survival of CRC patients with diabetes compared to those without diabetes could be the result of differences in treatment regimens. Although no difference has been observed in surgical rates between CRC patients with and without diabetes, it has been found that patients with diabetes are less likely to receive chemotherapy[12]. The decision to give adjuvant treatment is based on weighing the relative benefits of a treatment in terms of reducing risk of recurrence and improving survival against its potential side effects and complications[12]. Treatment efficacy and the presence of complications may affect survival rates as well (Figure 1).

A previous study of the Eindhoven Cancer Registry (ECR) revealed that CRC patients with diabetes are still receiving chemotherapy less often, although differences in treatment between CRC patients with and without diabetes are decreasing[27]. Furthermore, the proportion of stage II/III rectal cancer patients with and without diabetes who received radiotherapy was 58% and 75%, respectively, between 1999 and 2003, but this difference has more recently become smaller, with respective rates of 81% and 87%[27]. Chemotherapy is often not recommended for patients with significant comorbidities, such as diabetes, as such patients are likely to derive less benefit due to their limited life expectancy and higher risk of chemotherapy-induced toxicity[12,27] (Figure 1). Ensuring that every high-risk CRC patient is referred to a medical oncologist is a crucial step in the administration of chemotherapy as well as quality of care[51,52]. Whereas especially in older patients such a visit is often replaced by a visit to another clinician and, thus, suboptimal information, as the sole advisor and prescriber of chemotherapy, a visit to the medical oncologist is the only way to receive chemotherapy. In addition, once referred, studies have shown that older oncologists may have an approach that may be more conservative because of less-recent training, more experience with chemotherapy toxicity and/or a lesser tendency to generalize the results of clinical trials[53].

The patients themselves also play an important role in the decision to receive chemotherapy. It may be speculated that some patients, especially the elderly and those with diabetes, are less willing to accept the possible side effects of cancer treatment or have greater concerns about the negative effects that chemotherapy could have on their quality of life[54].

Although the beneficial effects of cancer treatment have been widely studied, the results in patients with comorbidities, such as diabetes have been rather less studied. Some studies of this patient population have found that CRC patients who received adjuvant cancer treatment had a better prognosis[55-57]. However, these studies are often prone to bias by selecting only the fittest patients and so may not be representative of all cancer patients with diabetes[58].

Cancer treatment response in diabetes patients

Diabetes may have a negative effect on cancer therapies. Cancer cells in patients with diabetes may be less sensitive to chemo/radiotherapy, resulting in higher rates of local tumour progression and lower rates of complete pathological response[12,59]. Also, the frequent presence of microvascular disease in patients with diabetes may reduce the release of radiosensitizing drugs in the hypoxic tumour environment[59]. Thus, research should focus on the effect of cancer treatment on the complete pathological response in patients with diabetes, taking into account detailed information on treatment dose, number and length of cycles, and possible dose adjustments.

Cancer treatment complications

Studies of complications in patients with diabetes after cancer treatment are limited and heterogeneous, and focus on various complications and 30-day mortality. Postoperative mortality or the 30-day mortality in most studies appeared to be higher in CRC patients with diabetes compared to those without diabetes, although the studies involved only small selected subgroups of patients[6,60-62]. Postoperative mortality in these patients could be higher due to infectious, cardiovascular and chemotherapy-related complications. Although the association between diabetes and infectious diseases was not confirmed in studies of complications after cancer treatment[6,7,62], one study found that high postoperative glucose levels were associated with higher risk of surgical site infections[63]. The cellular effects of hyperglycaemia on wound healing during the postoperative period may have influenced the risk of infection. However, even though diabetes is a risk factor for atherosclerosis, resulting in higher risk of myocardial infarction and cardiovascular disease, studies investigating cardiovascular complications after surgery in CRC patients have shown mixed results[6,7,61,62]. Some could find no association between

diabetes and cardiovascular complications, while others found higher risks of hepatic decompensation after liver surgery, acute myocardial infarction and anastomotic complications in CRC patients with diabetes compared to those without diabetes[6,7,61,62]. Also, higher anastomotic leak rates were seen in CRC patients with diabetes that could have been related to microvascular disease in those with diabetes[59,64].

Chemotherapy toxicity has been investigated to a lesser extent. One study reported a greater risk of severe treatment-related diarrhea after chemotherapy in colon cancer patients with compared to without diabetes, while the rates of other major toxicities were not significantly different[7]. Also, receiving adjuvant therapy was not associated with a greater probability of chemotherapy toxicity, defined as all-causes hospitalization rates after chemotherapy among colon cancer patients with diabetes[58]. Another study found that the dose of chemotherapy was reduced in 43% of colon cancer patients mostly because of gastrointestinal and neurological side effects, and was similar in those with and without diabetes[17].

Conclusions

Less administration of chemotherapy, more patient refusal of adjuvant treatment, lower rates of pathological response, higher postoperative mortality, and higher rates of infectious, cardiovascular and chemotherapy-related complications may be associated with lower overall survival rates in CRC patients with diabetes.

Diabetes treatment and control

Diabetes control

It may be hypothesized that some individuals perceive a diagnosis of CRC as more serious and life-threatening than diabetes, leading them to prioritize cancer treatment over appropriate diet, glucose monitoring and taking anti-diabetic medications as prescribed. The lack of attention to diabetes during cancer treatment may lie behind the variability of HbA_{1c} values and development of hyperglycaemia, hypoglycaemia or other diabetes complications that, in turn, can increase the risk of infections, hospitalizations and even mortality. One small study of CRC patients with diabetes revealed that those with well-controlled diabetes (HbA_{1c} <7.5%) had significantly better cancer-specific survival than those with poorly-controlled diabetes (HbA_{1c} ≥7.5%)[65].

Besides the lack of attention to diabetes treatment, the corticosteroids used in cancer treatment protocols can affect glucose levels directly and therefore influence the above-mentioned complications, as will hyperglycaemia indirectly[66-69].

Glucose-lowering drugs

CRC patients with diabetes treated with metformin as part of their anti-diabetic therapy appear to have superior overall rates of survival[70-74]. However, whether the observed benefits of metformin can be attributed to its use before and/or after the diagnosis of cancer is not clear. A methodological limitation of many studies of metformin and CRC outcomes is that they include the use of metformin as a dichotomous variable in the analyses. However, as the medications used by diabetes patients can vary considerably over time, the inclusion of cumulative exposures in the analysis would have been a more accurate way to investigate the effect of metformin on mortality[75]. Given these suboptimal study designs, the debate as to whether and to what extent metformin might influence the prognosis for CRC patients and be a candidate drug as an additional therapy to adjuvant chemotherapy is still ongoing.

In addition, the decision to use metformin to treat diabetes may have been influenced by clinical and metabolic factors that might have influenced the prognosis of CRC, leading to a situation in which metformin use may be associated with a better prognosis, but not responsible for it. While awaiting the results of randomized metformin trials[76,77], observational studies using a time-varying approach of cumulative drug duration are suggested.

Conclusions

The lack of attention to diabetes during cancer treatment may adversely affect diabetes control, resulting in lower overall survival, although the evidence is scanty. The debate as to whether or not the glucose-lowering drug metformin influences the prognosis of CRC is ongoing, as previous studies had many methodological complications.

Discussion

This comprehensive review highlights the complexity of the association between diabetes, CRC and patient survival. Several potential explanations have been proposed for the observed association between overall and CRC-specific survival and diabetes in CRC patients. New studies should account for all aspects of this association, including consideration of common risk factors and cancer stage and treatment differences, while focusing on tumour-related outcomes, such as recurrence and cancer-specific survival, as well as considering the effects of competing risks.

Understanding the relationship between diabetes, cancer and its prognosis may be considered one of the next challenges in this field, and new studies need to

account for the abundance of factors associated with having both diseases and survival. Once an association between diabetes, recurrence and cancer-related survival is established, the underlying mechanism may then be studied in greater detail.

References

1. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2011;26(11):863-76.
2. Kramer HU, Schottker B, Raum E, Brenner H. Type 2 diabetes mellitus and colorectal cancer: meta-analysis on sex-specific differences. Eur J Cancer. 2012;48(9):1269-82.
3. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679-87.
4. Deng L, Gui Z, Zhao L, Wang J, Shen L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. Dig Dis Sci. 2012;57(6):1576-85.
5. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754-64.
6. Jullumstro E, Kollind M, Lydersen S, Edna TH. Diabetes mellitus and outcomes of colorectal cancer. Acta Oncol. 2009;48(3):361-7.
7. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, 3rd, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003;21(3):433-40.
8. Stein KB, Snyder CF, Barone BB, Yeh HC, Peairs KS, Derr RL, et al. Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: a systematic review and meta-analysis. Dig Dis Sci. 2010;55(7):1839-51.
9. van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. Diabetologia. 2012;55(8):2163-72.
10. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol. 2011;30(1):53-9.
11. Polednak AP. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: a population-based study. Cancer Detect Prev. 2006;30(5):466-72.
12. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
13. Bella F, Minicozzi P, Giacomin A, Crocetti E, Federico M, Ponz de Leon M, et al. Impact of diabetes on overall and cancer-specific mortality in colorectal cancer patients. J Cancer Res Clin Oncol. 2013;139(8):1303-10.
14. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.
15. Jeon JY, Jeong DH, Park MG, Lee JW, Chu SH, Park JH, et al. Impact of Diabetes on Oncologic Outcome of Colorectal Cancer Patients: Colon vs. Rectal Cancer. PLoS One. 2013;8(2):e55196.
16. Huang YC, Lin JK, Chen WS, Lin TC, Yang SH, Jiang JK, et al. Diabetes mellitus negatively impacts survival of patients with colon cancer, particularly in stage II disease. J Cancer Res Clin Oncol. 2011;137(2):211-20.
17. van Waalwijk MA, van de Schans SAM, Haak HR, Extermann M, Dercksen MW, Janssen-Heijnen M. Diabetes alone should not be a reason for withholding adjuvant chemotherapy for stage III colon cancer. Journal of comorbidity. 2011;1:19-27.
18. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-32.
19. Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance? Stat Med. 2011;31(11-12):1089-97.
20. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. Epidemiology. 2009;20(4):555-61.
21. Flanders WD. Inaccuracies of death certificate information. Epidemiology. 1992;3(1):3-5.
22. Hinchliffe SR, Abrams KR, Lambert PC. The impact of under and over-recording of cancer on death certificates in a competing risks analysis: a simulation study. Cancer Epidemiol. 2013;37(1):11-9.
23. Richardson LC, Pollack LA. Therapy insight: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol. 2005;2(1):48-53.

24. Sullivan PW, Morrato EH, Ghushchyan V, Wyatt HR, Hill JO. Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000-2002. Diabetes Care. 2005;28(7):1599-603.

25. Nivel. LINH–Registration General Practitioners. Available at http://www.nivel.nl/incidentie-en-prevalentiecijfers-in-de-huisartsenpraktijk Last accessed 12 August 2013

26. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277-300.

27. Zanders MM, van Steenbergen LN, Haak HR, Rutten HJ, Pruijt JF, Poortmans PM, et al. Diminishing differences in treatment between patients with colorectal cancer with and without diabetes: a population-based study. Diabet Med. 2013;30(10):1181-8.

28. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55(6):1607-18.

29. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. Diabetes Care. 1999;22(11):1887-98.

30. Romaguera D, Guevara M, Norat T, Langenberg C, Forouhi NG, Sharp S, et al. Mediterranean diet and type 2 diabetes risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study: the InterAct project. Diabetes Care. 2011;34(9):1913-8.

31. Meyerhardt JA, Niedzwiecki D, Hollis D, Saltz LB, Hu FB, Mayer RJ, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA. 2007;298(7):754-64.

32. Pollak M. Do cancer cells care if their host is hungry? Cell Metab. 2009;9(5):401-3.

33. Cichosz SL, Fleischer J, Hoeyem P, Laugesen E, Poulsen PL, Christiansen JS, et al. Objective measurements of activity patterns in people with newly diagnosed Type 2 diabetes demonstrate a sedentary lifestyle. Diabet Med. 2013;30(9):1063-6.

34. Schienkiewitz A, Schulze MB, Hoffmann K, Kroke A, Boeing H. Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Am J Clin Nutr. 2006;84(2):427-33.

35. Campbell PT, Newton CC, Dehal AN, Jacobs EJ, Patel AV, Gapstur SM. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol. 2012;30(1):42-52.

36. Denost Q, Quintane L, Buscail E, Martenot M, Laurent C, Rullier E. Short- and long-term impact of body mass index on laparoscopic rectal cancer surgery. Colorectal Dis. 2012;15(4):463-9.

37. Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: A Meta-analysis of prospective cohort studies. Int J Cancer. 2013;133(8):1905-13.

38. Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol. 2006;24(22):3535-41.

39. Baade PD, Meng X, Youl PH, Aitken JF, Dunn J, Chambers SK. The impact of body mass index and physical activity on mortality among patients with colorectal cancer in Queensland, Australia. Cancer Epidemiol Biomarkers Prev. 2011;20(7):1410-20.

40. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

41. Fazio L, Cotterchio M, Manno M, McLaughlin J, Gallinger S. Association between colonic screening, subject characteristics, and stage of colorectal cancer. Am J Gastroenterol. 2005;100(11):2531-9.

42. De Marco MF, Janssen-Heijnen ML, van der Heijden LH, Coebergh JW. Comorbidity and colorectal cancer according to subsite and stage: a population-based study. Eur J Cancer. 2000;36(1):95-9.

43. Corkum M, Urquhart R, Kendell C, Burge F, Porter G, Johnston G. Impact of comorbidity and healthcare utilization on colorectal cancer stage at diagnosis: literature review. Cancer Causes Control. 2012;23(2):213-20.

44. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. Br J Cancer. 2009;101 Suppl 2:S92-S101.

45. Mitchell E, Macdonald S, Campbell NC, Weller D, Macleod U. Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. Br J Cancer. 2008;98(1):60-70.

46. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia. 2011;54(9):2263-71.

47. Lemmens V, van Steenbergen L, Janssen-Heijnen M, Martijn H, Rutten H, Coebergh JW. Trends in colorectal cancer in the south of the Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. Acta Oncol. 2010;49(6):784-96.

48. Limburg PJ, Anderson KE, Johnson TW, Jacobs DR, Jr., Lazovich D, Hong CP, et al. Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev. 2005;14(1):133-7.

49. He J, Stram DO, Kolonel LN, Henderson BE, Le Marchand L, Haiman CA. The association of diabetes with colorectal cancer risk: the Multiethnic Cohort. Br J Cancer. 2010;103(1):120-6.

50. Wray CM, Ziogas A, Hinojosa MW, Le H, Stamos MJ, Zell JA. Tumor subsite location within the colon is prognostic for survival after colon cancer diagnosis. Dis Colon Rectum. 2009;52(8):1359-66.

51. Luo R, Giordano SH, Freeman JL, Zhang D, Goodwin JS. Referral to medical oncology: a crucial step in the treatment of older patients with stage III colon cancer. Oncologist. 2006;11(9):1025-33.

52. Luo R, Giordano SH, Zhang DD, Freeman J, Goodwin JS. The role of the surgeon in whether patients with lymph node-positive colon cancer see a medical oncologist. Cancer. 2007;109(5):975-82.

53. Keating NL, Landrum MB, Klabunde CN, Fletcher RH, Rogers SO, Doucette WR, et al. Adjuvant chemotherapy for stage III colon cancer: do physicians agree about the importance of patient age and comorbidity? J Clin Oncol. 2008;26(15):2532-7.

54. Mols F, Beijers T, Lemmens V, van den Hurk CJ, Vreugdenhil G, van de Poll-Franse LV. Chemotherapy-Induced Neuropathy and Its Association With Quality of Life Among 2- to 11-Year Colorectal Cancer Survivors: Results From the Population-Based PROFILES Registry. J Clin Oncol. 2013;31(21):2699-707.

55. Iwashyna TJ, Lamont EB. Effectiveness of adjuvant fluorouracil in clinical practice: a population-based cohort study of elderly patients with stage III colon cancer. J Clin Oncol. 2002;20(19):3992-8.

56. Gill S, Loprinzi CL, Sargent DJ, Thome SD, Alberts SR, Haller DG, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol. 2004;22(10):1797-806.

57. Burdette-Radoux S, Muss HB. Adjuvant chemotherapy in the elderly: whom to treat, what regimen? Oncologist. 2006;11(3):234-42.

58. Gross CP, McAvay GJ, Guo Z, Tinetti ME. The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. Cancer. 2007;109(12):2410-9.

59. Caudle AS, Kim HJ, Tepper JE, O'Neil BH, Lange LA, Goldberg RM, et al. Diabetes mellitus affects response to neoadjuvant chemoradiotherapy in the management of rectal cancer. Ann Surg Oncol. 2008;15(7):1931-6.

60. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Postoperative mortality in cancer patients with preexisting diabetes: systematic review and meta-analysis. Diabetes Care. 2010;33(4):931-9.

61. Davila JA, Rabeneck L, Berger DH, El-Serag HB. Postoperative 30-day mortality following surgical resection for colorectal cancer in veterans: changes in the right direction. Dig Dis Sci. 2005;50(9):1722-8.

62. Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. J Gastrointest Surg. 2002;6(1):88-94.

63. McConnell YJ, Johnson PM, Porter GA. Surgical site infections following colorectal surgery in patients with diabetes: association with postoperative hyperglycemia. J Gastrointest Surg. 2009;13(3):508-15.

64. Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg. 1997;185(2):105-13.

65. Siddiqui AA, Spechler SJ, Huerta S, Dredar S, Little BB, Cryer B. Elevated HbA_{1c} is an independent predictor of aggressive clinical behavior in patients with colorectal cancer: a case-control study. Dig Dis Sci. 2008;53(9):2486-94.

66. Hershey DS, Given B, Given C, Corser W, von Eye A. Predictors of diabetes self-management in older adults receiving chemotherapy. Cancer Nurs. 2014;37(2):97-105.

67. Hershey DS, Tipton J, Given B, Davis E. Perceived impact of cancer treatment on diabetes self-management. Diabetes Educ. 2012;38(6):779-90.

68. Pentakota SR, Rajan M, Fincke BG, Tseng CL, Miller DR, Christiansen CL, et al. Does diabetes care differ by type of chronic comorbidity?: An evaluation of the Piette and Kerr framework. Diabetes Care. 2012;35(6):1285-92.

69. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. Diabetes Care. 2006;29(3):725-31.

70. Garrett CR, Hassabo HM, Bhadkamkar NA, Wen S, Baladandayuthapani V, Kee BK, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012;106(8):1374-8.

71. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299-304.

72. Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer. 2011;131(3):752-9.

73. Cossor FI, Adams-Campbell LL, Chlebowski RT, Gunter MJ, Johnson K, Martell RE, et al. Diabetes, metformin use, and colorectal cancer survival in postmenopausal women. Cancer Epidemiol. 2013;37(5):742-9.

74. Spillane S, Bennett K, Sharp L, Barron TI. A cohort study of metformin exposure and survival in patients with stage I-III colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2013;22(8):1364-73.

75. Stricker BH, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. Eur J Epidemiol. 2010;25(4):245-51.

76. http://www.clinicaltrials.gov, A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer, NCT01101438.

77. http://www.clinicaltrials.gov, A Trial of Standard Chemotherapy With Metformin (vs Placebo) in Women With Metastatic Breast Cancer, NCT01310231.

3

Effect of diabetes on endometrial cancer recurrence and survival

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Abstract

Objective: The purpose of this study was to investigate the influence of diabetes mellitus (DM) on cancer stage at diagnosis, cancer recurrence, and survival of endometrial cancer (EC) patients and the influence of the treatment of EC on glycaemic control, treatment, and complications of DM.

Methods: In this retrospective cohort study all 1,644 patients with EC newly diagnosed in 2000-2008 and recorded in the population-based Eindhoven Cancer Registry (ECR) were included. In addition, from this total cohort a subcohort was selected for additional data collection and analyses, including 193 EC patients with DM and an age-matched sample of 195 EC patients without DM. Patients with FIGO stage IV as well as non-endometrioid histology were excluded.

Results: In the total cohort EC patients with DM had a significantly higher age (69 years vs. 64 years), higher FIGO stages and more additional comorbidities compared to EC patients without DM. The 5-year overall survival rate for EC patients with DM was significantly lower than for EC patients without DM (68% vs. 84%). After adjusting for age, stage, period of diagnosis, cardiovascular disease, and treatment, this significant effect of DM on overall mortality persisted (HR 1.4; 95% CI 1.0−1.8). Subcohort analyses showed that EC patients with DM were diagnosed more often with a higher body mass index (BMI) (34 kg/m^2 vs. 30 kg/m^2) and EC was not significantly associated with changes in DM characteristics over time. Although the 5-year overall survival rate for EC patients with DM was significantly lower in the subcohort, for EC-specific mortality (n=388) no statistically significant effect of DM was observed after adjustment for FIGO stage (HR 1.7; 95% CI 0.7−3.9).

Conclusions: EC patients with DM compared to those without had worse patient characteristics, a higher FIGO stage, similar recurrence rates and worse overall survival.

Introduction

Endometrial cancer (EC), the most common of gynaecological malignancies, is suggested to be biologically associated with diabetes mellitus (DM), since shared risk factors, such as physical inactivity, obesity as well as high-saturated diet, only partly explain the observed higher risk of EC in DM patients[1-6]. Although the effect of DM on cancer risk may be small, given the high incidence of both DM and EC[7-9], even a modest association between DM and cancer means a considerable effect on public health. Furthermore, the number of newly diagnosed cancer patients with DM is expected to even double from 5500 in 2000 to 10,400 in 2015[10].

In addition, many studies showed that EC patients with pre-existing DM had a significantly increased overall mortality, while only one study investigated the effect of DM on EC-specific mortality[11-16]. This study found no effect of DM on EC-specific mortality, however, numbers of DM patients and deaths were small, and information about treatment of EC was missing[12]. The treatment of EC may affect glycaemic control, treatment, and complications of DM as well, whereas studies investigating this effect are lacking.

The potential biological link between the two diseases is incompletely understood and the mediators for this association are not known, but are thought to be related to hyperinsulinaemia (either due to insulin resistance or due to administered insulin), hyperglycaemia, insulin-like growth factor, and adipocytokines[3]. Moreover, evidence from observational studies suggest that some oral glucose lowering medications used to treat hyperglycaemia are associated with either increased or reduced cancer risk and mortality[17-18].

The purpose of the present study was to investigate whether EC patients with DM had a different stage at diagnosis, were treated differently, had different recurrence rates, and worse overall and EC-specific survival compared to EC patients without DM. In view of the association between EC and DM, the effect of treatment of EC on glycaemic control, treatment, and complications of DM was investigated as well.

Methods

Setting

The Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Centre South (CCCS), records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with 2.4 million inhabitants. The registry is notified by six pathology departments, hospital medical records offices in 10 community hospitals, and two large radiotherapy institutes.

Data on patient characteristics such as date of birth and postal code, as well as tumour characteristics such as date of diagnosis, tumour type, histology, stage, and initial treatment are routinely extracted from medical records by trained

registrars. The guideline for initial treatment of EC patients in the ECR region did change in our study period[19-20]. Between 1998 and 2004 five hospitals in the ECR region participated in a study about routine performance of pelvic lymphadenectomy for EC patients with FIGO stage I, these five were included in the total cohort and subcohort analysis[19]. For all EC patients with FIGO stage II radical hysterectomy with lymphadenectomy was advised in our region. Based on the results of the PORTEC I trial about radiotherapy, the EC guideline changed in 2000, only in the presence of two or three of the risk factors (>50% myometrial invasion, grade 3 histological type, age ≥60 years) adjuvant radiotherapy was advised[21].

Comorbidity is obtained from the medical records according to an adapted version of the Charlson Comorbidity Index[22]. Comorbidity was defined as life-shortening diseases that were present at the time of cancer diagnosis. Medication use served as indicator for active disease; comorbidity was registered when described in the medical record. DM included both type 1 and type 2 diseases and was registered as a dichotomous variable (yes/no), as were all other concomitant conditions. Tumour site and morphology were classified according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O)[23]. Socioeconomic status (SES), based on individual fiscal data on the economic value of the home and household income, was provided at an aggregated level for each postal code[24]. Information about vital status was obtained from the municipal personal records database (GBA) for all EC patients included in this study.

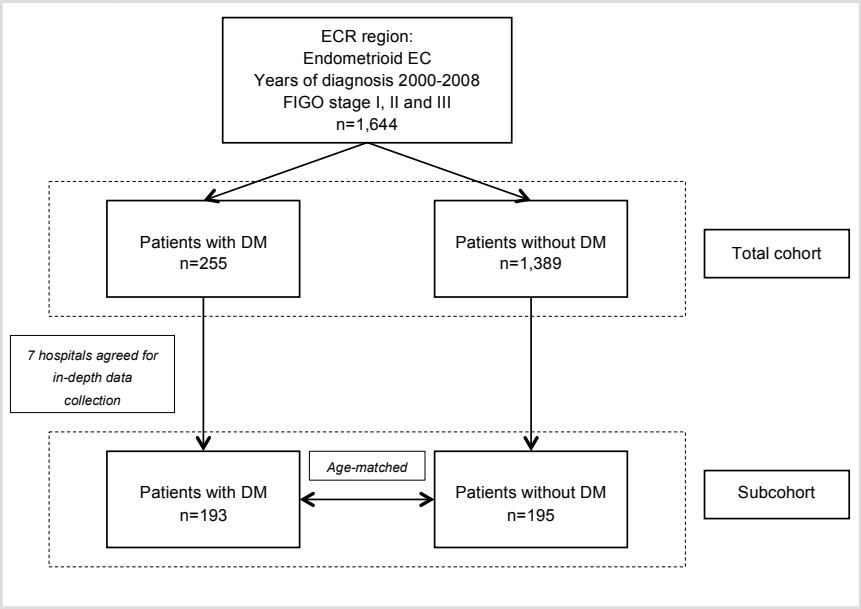
Total cohort

For this retrospective cohort study we included all patients with EC, newly diagnosed between 2000 and 2008 from the ECR (Figure 1). Only patients with endometrioid EC were selected because this type of EC is oestrogen driven and related to risk factors like obesity, hyperinsulinaemia, and DM[25]. We selected all patients with FIGO stages I, II, and III, according to the International Federation of Gynaecology and Obstetrics (FIGO, 1988)[26]. FIGO stage IV (n=58) was excluded because treatment differed with other FIGO stages and no effect of DM on prognosis was seen for this subgroup in earlier studies[15]. After selection a total of 255 EC patients with DM and 1,389 EC patients without DM remained for the total cohort analyses, using data from the ECR and GBA (Figure 1).

Subcohort

Out of the total cohort seven hospitals in the ECR region consented to provide additional in-depth data. This resulted in a selection of 193 EC patients with DM for the subcohort, they were matched on age, thereby selecting an age-matched group of 195 EC patients without DM for in-depth analyses. Matching for age was

Figure 1. Flowchart of the selection of endometrial cancer patients for the total cohort and subcohort.



DM, diabetes mellitus; EC, endometrial cancer; ECR, Eindhoven Cancer Registry.

randomly performed according to 5-year age groups.

For the subcohort data collection analysis we went back to the medical records and collected information about BMI, smoking status, complications after radiotherapy, type of DM, date of onset, and the presence of complications due to DM. These complications were registered as microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (coronary disease and peripheral arterial disease). To study the effect of EC on the regulation of DM, HbA_{1C} values, DM medication, and DM complications were registered in the year before diagnosis and the year after diagnosis of EC. Information about recurrence rate and cause of death was also collected from the medical records. Recurrence was defined as the existence of local (vaginal cuff) or regional recurrence (pelvis), or metastatic disease (lymph nodes and organs). Cause of death was obtained from the medical record when possible, otherwise it was determined by contacting the general practitioner. In addition, we also obtained information from the Registration System Oncological Gynaecology (ROGY), a web-based patient information system, maintained since 2006 by gynaecologists in the CCCS area[27]. Furthermore, we linked the patients of the subcohort with Pharmo RLS (Institute for Drug Outcomes Research) in order to obtain information about laboratory

tests, medication, and hospitalization[28].

Statistical analysis

The SAS computer package (version 9.2) was used for all statistical analyses (SAS Institute, Cary, NC, 1999). A p-value <0.05 was regarded as statistically significant. Differences between EC patients with and without DM in the total cohort and subcohort were analyzed using chi square and the t-test when applicable.

Overall survival analysis of the total cohort and subcohort was analyzed using the life-table method to evaluate prognosis after diagnosis of EC for patients with or without DM. Survival time was defined as the time from diagnosis to death or January 1, 2010 for the patients who were still alive. In the total cohort, survival was also analyzed according to FIGO stage at diagnosis and DM status.

The independent prognostic effect of DM on overall survival of EC patients was estimated using Cox proportional hazard analyses. The effect of DM over time satisfied the assumption of proportionality since the graphs of the log(log(survival)) versus log of survival time resulted in graphs with parallel lines. The hazard rates for death of EC patients with DM compared to EC patients without DM were further adjusted for age, stage, period of diagnosis, specific comorbidities, and treatment.

In addition, in the subcohort EC-specific survival and recurrence free survival was analyzed. EC-specific survival was analyzed using the life-table method to evaluate prognosis after diagnosis of EC, with EC-specific death as event, while censoring other causes of death. The hazard rates for death due to EC, comparing EC patients with and without DM, were further adjusted for stage. Recurrence free survival of EC patients with DM compared to without DM was analyzed as well. This survival was defined as time to the first recurrence or death from any cause, whichever occurred first.

Results

Total cohort

In the period 2000-2008, 1,644 women were diagnosed with EC, 255 (16%) of whom had DM at cancer diagnosis. EC patients with DM were on average 5 years older, diagnosed more often with a higher FIGO stage, and a lower SES (Table 1). Cardiovascular disease, hypertension, cerebrovascular disease, and pulmonary disease were more often present in EC patients with DM compared to EC patients without DM. Although EC patients with DM received surgery with lymphadenectomy less often, the number of positive lymph nodes did not differ between both groups (Table 1). EC patients with DM received radiotherapy more often compared to EC patients without DM.

At the end of follow-up, out of the total cohort 82 (31%) EC patients with DM died compared to 228 (16%) without DM. The 5-year overall survival rate for EC patients

Table 1. Characteristics of patients with EC FIGO stage I-III according to DM status (n=1,644).

	Total cohort (n=1,644)				Subcohort (n=388)			
	Without DM n=1,389		With DM n=255		Without DM n=195		With DM n=193	
	n	(%)	n	(%)	n	(%)	n	(%)
Mean age (± SD)	64	(± 10.3)	69	(± 9.1)**	69	(± 8.5)	70	(± 9.0)
FIGO stage [a]								
I	1158	(83)	190	(75)	160	(82)	135	(70)
IA	187	(16)	23	(12)	22	(14)	19	(14)
IB	610	(53)	97	(51)	75	(47)	68	(50)
IC	350	(31)	69	(37)	63	(39)	48	(36)
II	103	(8)	28	(11)	11	(6)	24	(12)
III	128	(9)	37	(14) *	24	(12)	34	(18) *
Grade EC [a]								
I	588	(44)	113	(45)	68	(37)	81	(43)
II	546	(41)	96	(39)	80	(44)	71	(38)
III	191	(15)	41	(16)	35	(19)	36	(19)
Socioeconomic status [a]								
Low	331	(24)	92	(37)	56	(29)	76	(41)
Middle	532	(39)	91	(37)	74	(38)	66	(35)
High	442	(33)	50	(20)	56	(29)	32	(17)
Institutionalized	59	(4)	15	(6) **	7	(4)	13	(7) *
Comorbidities [a]								
Cardiovascular disease	180	(15)	83	(33) **	44	(23)	68	(35) *
Hypertension	359	(30)	142	(56 **	77	(40)	111	(57) *
Cerebrovascular disease	32	(3)	17	(7) *	5	(3)	16	(8)*
Pulmonary disease	54	(5)	21	(8) *	7	(4)	19	(10) *
Previous cancer	159	(13)	35	(14)	28	(14)	28	(14)
Received surgery	1373	(99)	250	(98)	192	(98)	188	(97)
Type of surgery								
With lymphadenectomy	421	(30)	57	(22)	67	(34)	57	(30)
Positive lymph nodes	34	(8)	5	(9)	5	(7)	5	(9)
Without lymphadenectomy	968	(70)	198	(78) *	128	(66)	136	(70)
Received chemotherapy	27	(2)	2	(1)	2	(1)	1	(1)
Received radiotherapy	384	(28)	98	(38) *	62	(32)	73	(38)
Type of radiotherapy								
External beam radiotherapy	227	(16)	56	(22)	38	(19)	38	(20)
Brachytherapy	70	(5)	24	(9)	9	(5)	18	(9)
Combination	79	(6)	15	(6)	13	(7)	14	(7)
BMI (kg/m^2, ± SD) [a]	n.a.				30.1	(± 6.7)	33.7	(± 7.3) *
<25					56	(50)	42	(33)
30-35					30	(27)	36	(29)
>35					26	(23)	47	(38) *
Smoking status[a]	n.a.							
Yes					11	(11)	14	(14)
No					76	(75)	81	(79)
Quit					14	(14)	8	(8)

DM, diabetes mellitus; EC, endometrial cancer; [a] Does not add up to total due to missings, percentages determined for available data; * p<0.05; ** p<0.0001.

with DM was significantly lower than for EC patients without DM (68% vs. 84%) (Figure 2). After adjusting for age, stage, period of diagnosis, specific comorbidities, and treatment, this significant effect of DM on overall survival persisted (HR 1.3; 95% CI 1.0–1.8) (Table 3).

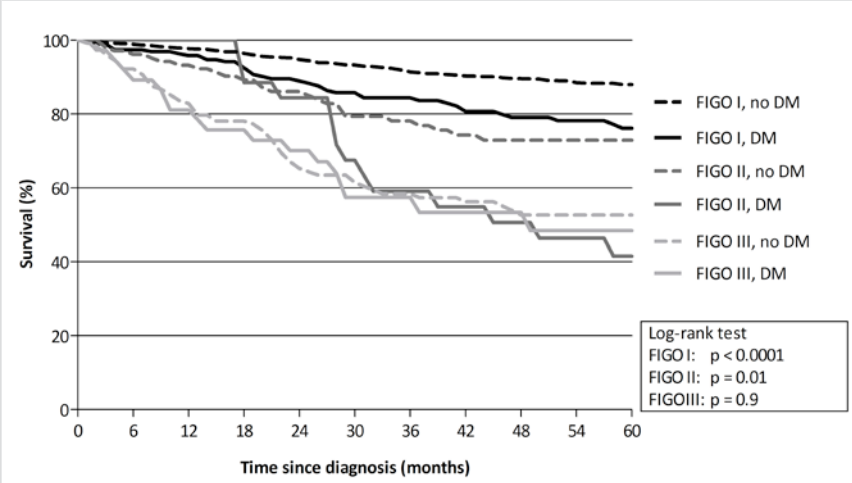
Subcohort

The patient characteristics of the subcohort of 388 EC patients were comparable to those in the total cohort. However, the percentage of EC patients who received lymphadenectomy and the proportion of additional comorbidities was higher compared to the percentage in the total cohort (Table 1). The in-depth data showed that EC patients with DM were diagnosed more often with a higher BMI compared to EC patients without DM, while smoking status did not differ between the two groups (Table 1).

The average duration of DM was nine years and nine patients were diagnosed with DM in the year before or at diagnosis of EC (Table 2). Mean HbA_{1c} values, BMI, and number of patients using medication remained almost similar from the year before up to one year after diagnosis of EC. Fifty-nine patients (30%) had one or more DM-related complications at the time of EC diagnosis and after EC diagnosis, 16 patients, without complications before diagnosis, developed micro- or macrovascular complications (Table 2).

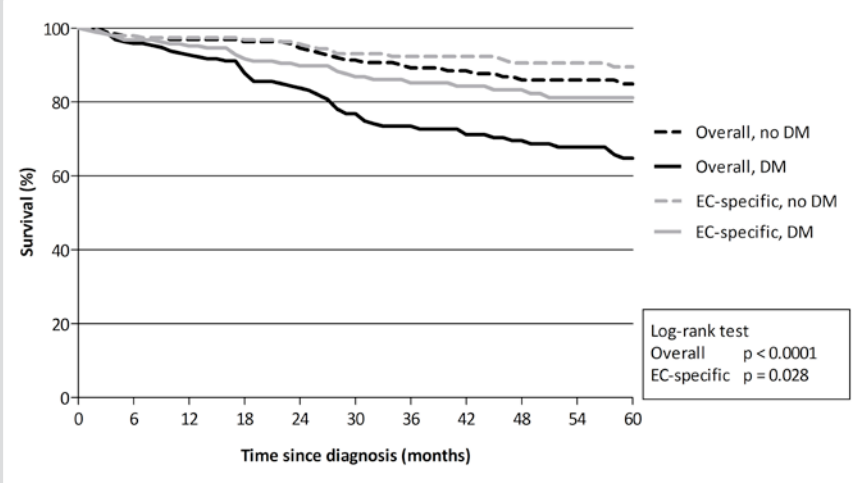
In the survival analysis of the subcohort, the 5-year overall survival rate for EC patients with DM was significantly lower than for EC patients without DM (65% vs. 85%). After adjusting for age, stage, period of diagnosis, specific comorbidities, and treatment, this significant effect of DM on overall survival persisted (HR 2.3; 95% CI 1.4–3.7) (Table 3). In contrast, for EC-specific mortality (n=388) no statistically significant effect of DM was observed after adjustment for FIGO stage (HR 1.4; 95% CI 0.7–2.6) (Table 3 and Figure 3). Although not statistically significant, evaluation of the cause of death showed that EC patients with DM died of comorbidity most often (n=33, 54%), whereas EC patients without DM died of EC (n=16, 57%) most often. Comorbidity included all different types of comorbid diseases present in the Charlson Comorbidity Index. In the group of comorbidities, cardiovascular and cerebrovascular diseases were the most common causes of death in EC patients (23% in patients with DM and 25% in patients without DM).
In the selected subcohort recurrent disease was found in 26 (14%) EC patients with DM compared to 27 (14%) without DM. Metastasis was the most frequent type of recurrence and was observed in 9% of EC patients with DM and 8% of EC patients without DM. Recurrence free survival was significantly lower for EC patients with DM compared to those without (p=0.0001). However, the difference between overall survival and recurrence free survival, was approximately the same for

Figure 2. Overall survival of EC patients according to DM status and FIGO stage.



DM, diabetes mellitus; EC, endometrial cancer.

Figure 3. Overall and EC-specific survival of EC patients according to DM status.



DM, diabetes mellitus; EC, endometrial cancer.

Table 2. DM characteristics before and after diagnosis of EC for patients with DM at cancer diagnosis (n=388).

	Before diagnosis [a]		After diagnosis [b]	
	n=193		n=193	
	n	(%)	n	(%)
DM type				
1	2	(1)		
2	191	(99)		
DM length at diagnosis (years, ± SD)	8.7	(± 7.7)		
<1	9	(5)		
1	7	(4)		
2-5	41	(21)		
5-10	40	(21)		
>10	45	(23)		
Unknown	51	(26)		
BMI mean (kg/m^2, ± SD)	34.1	(± 6.9)	33.3	(± 6.7)
Hba_{1c} mean (%,± SD)	7.6	(± 1.3)	7.5	(± 1.3)
Medication				
Oral glucose-lowering	105	(55)	99	(51)
Insulin	22	(11)	24	(13)
Diet	2	(1)	1	(1)
Oral glucose-lowering and insulin	38	(20)	47	(24)
No medication	3	(1)	2	(1)
Unknown	23	(12)	20	(10)
Complications				
Microvascular	8	(4)	11	(6)
Macrovascular	41	(21)	49	(25)
Both	10	(5)	15	(8)
No complications	92	(48)	76	(39)
Unknown	42	(22)	42	(22)

DM, diabetes mellitus; EC, endometrial cancer; [a] In the year before diagnosis of EC, until diagnosis; [b] From diagnosis of EC, until 1 year after diagnosis.

patients with and without DM. The recurrence did not differ between EC patients with and without DM, while the overall survival did differ strongly between both groups.

Discussion

In the present study, we found that EC patients with DM had a significantly higher overall mortality than those without DM. In addition, DM was not associated with higher recurrence rates, or a higher EC-specific mortality after adjustment for the observed higher FIGO stages found for patients with DM. DM treatment and DM complications did not change significantly when patients were compared before and after EC diagnosis and treatment.

Table 3. Multivariate regression analysis of the effect of diabetes on all-cause mortality and EC-specific mortality.

	Total cohort (n=1,644)		Subcohort (n=388)			
	All-cause mortality [a]		All-cause mortality [a]		EC-specific mortality [b]	
	HR [c]	(95% CI)	HR [c]	(95% CI)	HR [c]	(95% CI)
DM						
Yes	1.3	(1.0-1.8) *	2.3	(1.4-3.7) *	1.4	(0.7-2.6)
No	1.0		1.0		1.0	
Age	1.1	(1.1-1.1) **	1.1	(1.0-1.1) **		
FIGO						
Stage I	1.0		1.0			
Stage II	2.0	(1.4-2.9) *	2.0	(1.1-3.7) *	6.9	(3.1-15.4) **
Stage III	3.7	(2.7-5.2) **	3.8	(2.1-6.8) **	8.7	(4.3-17.5) **
Period of diagnosis	1.0	(0.9-1.1)	1.0	(1.0-1.2)		
Comorbidities [d]						
Cardiovascular disease	0.9	(0.7-1.3)	0.9	(0.6-1.6)		
Hypertension	0.9	(0.7-1.3)	0.8	(0.5-1.3)		
Cerebrovascular disease	2.0	(1.2-3.3) *	2.5	(1.2-5.1) *		
Pulmonary disease	1.3	(0.8-2.1)	1.1	(0.5-2.5)		
Previous cancer	1.7	(1.2-2.3) *	1.0	(0.6-1.8)		
Surgery						
Yes	1.0		1.0			
No	3.4	(2.0-5.7) **	4.1	(1.7-9.8) *		
Radiotherapy						
Yes	1.0		1.0			
No	1.0	(0.7-1.3)	1.5	(0.9-2.4)		

DM, diabetes mellitus; EC, endometrial cancer; [a] Proportional hazards model for all-cause mortality is adjusted for DM, age at time of diagnosis, FIGO stage, period of diagnosis, cardiovascular disease, hypertension, cerebrovascular disease, pulmonary disease, previous cancer, surgery, and radiotherapy; [b] Proportional hazards model for EC-specific mortality is adjusted for DM and FIGO stage; [c] HR = Hazard Ratio, missing values were included in the multivariate analysis, but not shown in the table; [d] The reference for a specific comorbidity is the absence of the specific comorbidity; * p<0.05; ** p<0.0001.

Previous studies have already identified DM as a prognostic factor for EC in postmenopausal patients[11-16]. In one of these, a Dutch population-based study, the hazard ratio was 1.4 (95% CI 1.1−1.8), while in another study of 93 DM patients a HR of 1.7 (95% CI 1.1−2.5) was found when comparing EC patients with and without DM[12,15]. However, in these studies no association between EC-specific mortality and DM was found. Cause of death has never been properly investigated for patients with EC, making it difficult to understand whether the observed increased overall mortality can simply be explained by an effect of DM or is a true effect due to interaction between the two diseases.

While in our study EC patients with DM had a higher FIGO stage at diagnosis compared to patients without DM, in other studies baseline DM was not associated

with the extent of disease at EC diagnosis[13,14]. At diagnosis the tumour has infiltrated the myometrium, causing postmenopausal blood loss as first symptom in 95% of EC patients, these symptom might be overshadowed by symptoms of comorbidities or ignored in DM patients[29]. In contrast, we hypothesized that DM affects myometrial invasion directly by a proliferative or anti-apoptotic effect, resulting in blood loss in a more advanced stage. This myometrial invasion may be effected by adipokines, which are adipocyte-secreted hormones, as well[30,31]. The plasma concentrations of adiponectin, one of the most abundant adipokines, are reduced in obese individuals and interestingly have been reported to have anticarcinogenic properties either. Furthermore, in vitro studies have shown that adiponectin may inhibit cell proliferation and induce apoptosis of some cancer cells. This may explain why EC patients with DM, and a significant higher BMI and thus lower adiponectin concentrations, have a more advanced tumour stage than their counterparts[30,31]. Other underlying biological factors are oestrogen, insulin, and the free related insulin-like growth factor-I (IGF-I), which may influence the effect of DM on EC[3,5]. Cancer proliferation might be stimulated by IGF-I, a biologically active form of growth factor[3]. Moreover, many cancer cells have an increased insulin receptor content, therefore insulin could favour cancer progression and facilitate the growth of tumours and early infiltration[3,32]. In contrast with insulin, the DM drug metformin is thought to be a potent inhibitor of cell proliferation in EC, thereby reducing cancer risk[33]. Whether the underlying mechanism for this effect is related to the systemic action of this drug, by reducing circulating insulin levels, or a direct action on cancer cells is still unknown[33].

Although the rapid tumour growth by insulin could explain the more advanced FIGO stages, an effect on presence of recurrence should than be expected as well. Even though our EC-specific survival analysis showed no effect of DM after adjusting for this more advanced tumour stage, another study did observe lower EC-specific survival for EC patients with DM[13]. However, this study analyzed only a small group of 42 EC patients with DM and no stratification for FIGO stage was made[13]. Another study, with 12,000 EC patients, investigated the impact of race and comorbidity on EC-specific survival, thereby adjusting for patients, tumour, and treatment characteristics[34]. DM was associated with poorer survival in white women, but not in blacks[34].

In our study the hypothesis that EC has a negative effect on the course of DM can be rejected when comparing values one year before and up to one year after diagnosis of EC. Although assuming that when a patient has EC, attention for DM control decreases, EC itself might have an effect on DM. In contrast, weight loss due to cancer, cancer therapy, and eating less may improve DM control. In contrast,

many breast cancer patients gain weight after diagnosis, resulting in a dysregulation of DM[35]. Since all of the abovementioned hypotheses may affect DM status in different ways, an overall effect could possibly be camouflaged.

A limitation of the current study is the retrospective study design, therefore only information available in the medical records could be collected, BMIs and HbA_{1c} values were not always reported. The BMI was missing in 39% of the EC patients in the subcohort. Furthermore, detailed information on DM medication was missing, which could be of interest when investigating the specific effect of metformin on survival in EC patients. The effect of DM on overall survival in the subcohort was suggested to be slightly stronger than in the total cohort. Although an explanation for this difference was not found, the number of patients in this cohort was small. A significant effect of DM on EC-specific mortality was not found, however, the additional analysis for EC-specific mortality was underpowered due to the relatively small number of patients in the subcohort. Therefore, the possible effect of DM on FIGO stage and EC-specific mortality has to be further investigated in a larger group of patients.
Although the total cohort and subcohort had almost similar baseline characteristics, the proportion of EC patients who received lymphadenectomy was higher in the subcohort. The seven hospitals selected for the subcohort analysis participated in a Dutch study about pelvic lymphadenectomy between 1998 and 2004[19], in which all EC patients with FIGO stage I received this therapy. Furthermore, the proportion of additional comorbidities, especially cardiovascular disease and hypertension, in EC patients without DM was higher in the subcohort compared to the total cohort, probably because the older age in the subcohort was associated with a higher number of comorbid conditions[36].

In summary, this study supports the hypothesis that EC patients with DM have worse survival rates than EC patients without DM. Higher FIGO stages and more comorbidities in EC patients with DM could explain these survival rates. Future studies are needed to reveal the relationship between DM and EC, explaining the late onset of symptoms in EC patients with DM compared to EC patients without DM. The higher mortality rates for EC patients with DM were most likely caused by DM as such, therefore, physicians should be encouraged and motivated to rigorously treat and follow these patients with DM also after the EC diagnosis and treatment. Furthermore, postmenopausal women with the combination of DM and EC might have a more advanced stage at EC diagnosis, resulting in a higher EC-specific mortality, so caution is recommended for this subgroup.

References

1. Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. Gynecol Oncol. 2009;114(1):121-7.
2. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50(7):1365-74.
3. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.
4. Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer. 2008;98(9):1582-5.
5. Wedisinghe L, Perera M. Diabetes and the menopause. Maturitas. 2009;63(3):200-3.
6. Bray F, Dos Santos Silva I, Moller H, Weiderpass E. Endometrial cancer incidence trends in Europe: underlying determinants and prospects for prevention. Cancer Epidemiol Biomarkers Prev. 2005;14(5):1132-42.
7. Sloan FA, Bethel MA, Ruiz D, Shea AM, Feinglos MN. The growing burden of diabetes mellitus in the US elderly population. Arch Intern Med. 2008;168(2):192-9; discussion 9.
8. Cancer in the Netherlands till 2020 (2011) Trends and prognoses. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-00-8.
9. Baan CA, Schoemaker CG, Jacobs-van der Bruggen MAM, Hamberg-van Reenen HH, Verkleij H, Heus S, et al. Diabetes tot 2025; preventie en zorg in samenhang. RIVM-rapport 260322004. 2009.
10. Cancer in the Netherlands (2004) Trends, prognoses and implications for healthcare. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-13-0.
11. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754-64.
12. Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. Int J Gynecol Cancer. 2007;17(2):441-6.
13. Folsom AR, Anderson KE, Sweeney C, Jacobs DR, Jr. Diabetes as a risk factor for death following endometrial cancer. Gynecol Oncol. 2004;94(3):740-5.
14. Steiner E, Eicher O, Sagemuller J, Schmidt M, Pilch H, Tanner B, et al. Multivariate independent prognostic factors in endometrial carcinoma: a clinicopathologic study in 181 patients: 10 years experience at the Department of Obstetrics and Gynecology of the Mainz University. Int J Gynecol Cancer. 2003;13(2):197-203.
15. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
16. Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008. Eur J Cancer. 2011;47(10):1504-10.
17. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55(6):1607-18.
18. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-32.
19. Zuurendonk LD, Smit RA, Mol BW, Feijen HW, de Graaff J, Sykora D, et al. Routine pelvic lymphadenectomy in apparently early stage endometrial cancer. Eur J Surg Oncol. 2006;32(4):450-4.
20. www.oncoline.nl. National Dutch guideline of endometrial cancer. 2011.
21. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355(9213):1404-11.
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

23. International Classification of Diseases of Oncology. Version 2013; first edition Geneva: WHO, 1976.

24. van Duijn C, Keij I. Sociaal-economische status indicator op postcode niveau. Maandstatistiek van de bevolking. 2002;50(2):32-5.

25. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-7.

26. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95 Suppl 1:S105-43.

27. Boll D, Hermans RHM, Keijser KGG, van der Putten HWHM, Vos MC, Kruitwagen RFPM, et al. Nuttige Diensten van Regionaal EPD, Bundeling Regionale Expertise Gynaecologische Oncologie. Medisch Contact. 2009;64(21):942-5.

28. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395-404.

29. Kurman RJ, Ellenson LH, Ronnett BM. Blaustein's Pathology of the Female Genital Tract. 6th ed. New York, NY: Springer-Verlag; 2011.

30. Moon HS, Chamberland JP, Aronis K, Tseleni-Balafouta S, Mantzoros CS. Direct role of adiponectin and adiponectin receptors in endometrial cancer: in vitro and ex vivo studies in humans. Mol Cancer Ther. 2011;10(12):2234-43.

31. Cust AE, Kaaks R, Friedenreich C, Bonnet F, Laville M, Lukanova A, et al. Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women. J Clin Endocrinol Metab. 2007;92(1):255-63.

32. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009;16(4):1103-23.

33. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation--implications for a novel treatment strategy. Gynecol Oncol. 2010;116(1):92-8.

34. Olson SH, Atoria CL, Cote ML, Cook LS, Rastogi R, Soslow RA, et al. The impact of race and comorbidity on survival in endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2012;21(5):753-60.

35. Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. Cancer. 2012;118(8 Suppl):2277-87.

36. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol. 2005;55(3):231-40.

4

Diminishing differences in treatment between colorectal cancer patients with and without diabetes: a population-based study

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Abstract

Aims: An increasing number of oncologists will be confronted with individuals having diabetes and cancer. We assessed changes in patient-, tumour-, and treatment- related variables in colorectal cancer (CRC) patients with and without diabetes.

Methods: All 17,170 cases of primary CRC between 1995 and 2010 in the South-Eastern Netherlands were included. The Cochrane-Armitage test and logistic regression analysis were used to analyse trends.

Results: 11,893 patients were diagnosed with colon cancer and 5,277 with rectal cancer, of whom 1,711 (14%) and 609 (12%), respectively, had diabetes at the time of cancer diagnosis. CRC patients with diabetes compared to those without were about 5 years older and more often diagnosed with proximal colon tumours (60% vs. 54%, $p<0.0001$). Chemotherapy administration significantly increased in stage III colon cancer patients with and without diabetes (from 17% in 1995-1998 to 50% in 2007-2010, 38% to 63%, respectively, $p<0.0001$). However, in the most recent period and after adjusting for the co-variables age, gender, year of diagnosis, and specific comorbidities, stage III colon cancer patients with diabetes received adjuvant chemotherapy less frequently than those without (OR 0.7; 95% CI 0.5-0.9; $p=0.002$). The proportion of stage II/III rectal cancer patients with and without diabetes who underwent radiotherapy was similar in recent years (91% vs. 87%).

Conclusions: Although the administration of chemotherapy and radiotherapy increased between 1995 and 2010 in CRC patients with and without diabetes, CRC patients with diabetes continue to receive chemotherapy less frequently than those without diabetes.

Introduction

Numerous epidemiological studies have shown that colorectal cancer (CRC) occurs more commonly in individuals with type 2 diabetes than in the general population [1-3]. The number of newly diagnosed CRC patients, of whom 11-15% have diabetes as well, is estimated to increase from 12,755 in 2010 to 17,000 in 2020 in the Netherlands[4-6]. Although the effect of diabetes on CRC risk may be small, given the increasing prevalence of both diabetes and CRC, even a modest association between the two diseases indicates a considerable effect on public health.

Due to the high prevalence of diabetes and cancer, the American Diabetes Association and American Cancer Society recently reviewed the scientific literature concerning the influence of diabetes on cancer diagnosis, treatment and outcome[3]. This consensus report recommended focusing on site-specific cancers instead of combining all sites[3]. CRC patients with diabetes have worse survival rates than those without diabetes, which is hypothesised to be the result of less aggressive cancer treatment for diabetic individuals[6-8]. Although no specific data are available on the trends in treating CRC patients with diabetes, previous studies have shown that elderly CRC patients are being increasingly treated with a more aggressive approach, resulting in increased survival[9,10]. In the last decades, a strong improvement in survival was observed in patients with stage III colon cancer, which was most likely related to the increased administration of adjuvant chemotherapy[9-12]. In rectal cancer patients, the introduction of the total mesorectal excision (TME) technique, the widespread introduction of neo-adjuvant radio-(chemo) therapy and the shift from postoperative to preoperative radiotherapy might have improved survival rates[13,14].

In this study, we analysed trends in diabetes prevalence among CRC patients, and compared trends in the treatment of CRC patients with and without diabetes in the period between 1995 and 2010.

Methods

Data collection

The Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Centre South (CCCS), records data on all patients newly diagnosed with cancer in the South-Eastern part of the Netherlands, an area with 2.4 million inhabitants. The registry is notified by six pathology departments, 10 community hospitals (at 17 locations), and two large radiotherapy departments. Trained registration clerks actively collect data on diagnosis, staging, and detailed information about initial treatment from hospital medical records. Stage is based on the pathological TNM classification[15]. In rectal cancer patients, the pathological TNM stages II and III are combined for the analyses of preoperative radiotherapy and T3 and T4 tumours are combined for the analyses of chemo-radiation. Since 1995, the ECR has

recorded comorbidity from the medical records according to a slightly adapted version of the Charlson Comorbidity Index[16]. The use of medication serves as an indicator for active disease, but comorbidity is only registered when it is described in the medical record and is present at the time of cancer diagnosis. Diabetes includes both type 1 and type 2 diseases, and is registered as a dichotomous variable (yes/no), like all the other concomitant conditions. Patients treated with diabetes medication as well as with only dietary measures are registered as having diabetes. Completion of registration takes place about nine months after diagnosis. The quality of data is high and the completeness is estimated to be at least 95%[17]. For the present study, all patients with primary colorectal cancer (C18 and C20) were included, while patients with unknown site (C18.8-18.9; 1% of total) and unknown stage of the primary tumour, cases diagnosed by autopsy alone and patients with rectosigmoid tumours (C19) were excluded. Rectosigmoid tumours were excluded, since the treatment decisions in this subtype are inconsistent and are sometimes treated as a colon and sometimes as a rectal tumour. Oncological treatment was defined as surgery, radiotherapy, chemotherapy, and chemo-radiation. Surgery included resection of the primary tumour with or without lymph node resection. CRC patients with missing data on diabetes status were excluded (8% of total). Patients were divided into those with and without diabetes for all analyses. The study period was divided into four categories: 1995-1998, 1999-2002, 2003-2006, and 2007-2010. Tumour localisation was categorised into anatomical subsites: proximal colon, consisting of the caecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0-C18.5); distal colon, consisting of the descending colon and sigmoid colon (C18.6-C18.7); and rectum, consisting of the rectum (C20).

Statistical analyses

All analyses were stratified for colon and rectal cancer patients. Diabetes prevalence rates are shown as 3-year moving averages. Differences in patient characteristics and treatment between CRC patients according to diabetes status were determined using chi square and t-test when applicable. The proportion of patients receiving treatment was reported according to the diabetes status, stage, and period of diagnosis. Differences in patient characteristics and treatment over time between CRC patients with and without diabetes were tested by the Cochrane-Armitage trend test and linear regression (only for mean age). Multivariable logistic regression analysis was conducted to examine determinants of receiving chemotherapy, chemo-radiation, and radiotherapy in colon and rectal cancer patients. Variables of interest included in the multivariable analysis were: diabetes, age, gender, cardiovascular disease, hypertension, previous cancer, pulmonary disease, cerebrovascular disease, and period of diagnosis. Effect modification

between diabetes and confounding variables was assessed by adding interaction terms diabetes*confounding variable in the multivariable logistic regression analysis. A p-value <0.05 was considered statistically significant.
The SAS computer package (SAS system 9.2, SAS Institute, Cary, NC) was used for all analyses.

Results

Between 1995 and 2010, 17,170 cases of colon and rectal cancer were diagnosed in the ECR area. Of all 11,893 colon and 5,277 rectal cancer patients, 1,711 (14%) and 609 (12%), respectively, had diabetes at the time of CRC diagnosis. Diabetes prevalence among patients with CRC increased from 9% in 1995 to 17% in 2010 (p<0.0001) (Figure 1). The age-standardisation of these prevalence rates resulted in a comparable graph, but since the crude prevalence of diabetes shows the true burden of health care best, only the crude rates were shown. CRC patients with diabetes were on average 5 years older compared to those without diabetes. In time, more patients had two or more comorbidities at the time of CRC diagnosis (Table 1). Furthermore, the proportion of patients with stage IV disease increased and with stage II disease decreased in both colon and rectal cancer patients with and without diabetes (Table 1). Colon cancer patients with diabetes more often had a tumour located in the proximal colon compared to those without diabetes (60% vs. 54%, p<0.0001).

Figure 1. Trends in prevalence of diabetes at the time of colon and rectal cancer diagnosis (n=17,170).

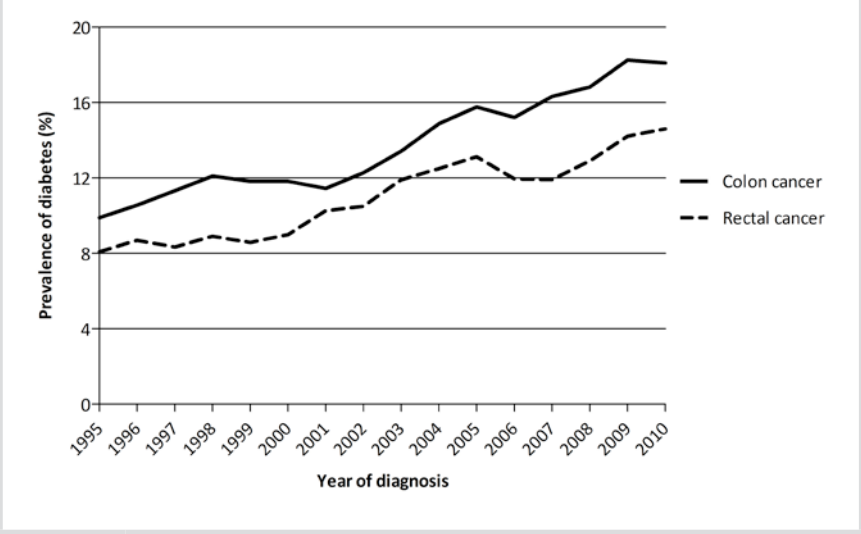


Table 1. Patient and tumour characteristics for colorectal cancer patients with and without diabetes (n=17,170).

	Colon cancer (n=11,893)				Rectal cancer (n=5,277)			
	Diabetes (n=1,711)		No diabetes (n=10,182)		Diabetes (n=609)		No diabetes (n=4,668)	
	n	(%)	n	(%)	n	%	n	%
Age (years)								
Mean (SD)	73	(9)	69	(11) **	71	(9)	66	(12) **
≥ 75 years	799	(47)	3579	(35) **	240	(39)	1222	(26) **
Gender								
Male	820	(48)	5259	(52)	372	(61)	2835	(61)
Female	891	(52)	4923	(48) *	237	(39)	1833	(39)
Comorbidities								
None	320	(19)	4049	(40)	126	(21)	2118	(45)
1	591	(34)	3365	(33)	234	(38)	1512	(33)
≥2	800	(47)	2768	(27) **	249	(41)	1038	(22) **
Five most frequent comorbidities:								
Cardiovascular disease	811	(47)	2899	(28) **	253	(42)	1089	(23) **
Hypertension	806	(47)	2469	(24) **	276	(45)	1072	(23) **
Previous cancer	288	(17)	1597	(16)	99	(16)	610	(13) *
Pulmonary disease	212	(12)	1002	(10) *	67	(11)	456	(10)
Cerebrovascular disease	154	(9)	449	(4) **	45	(7)	177	(4) **
TNM stage[15]								
I	266	(16)	1633	(16)	173	(29)	1405	(30)
II	659	(38)	3658	(36)	164	(27)	1168	(25)
III	430	(25)	2670	(26)	160	(26)	1146	(25)
IV	356	(21)	2221	(22)	112	(18)	949	(20)
Type of tumour								
Proximal colon [a]	1025	(60)	5503	(54)				
Distal colon [a]	686	(40)	4679	(46) **				
Period of diagnosis								
1995-1998	244	(14)	1957	(19)	78	(13)	834	(18)
1999-2002	300	(18)	2287	(22)	105	(17)	974	(21)
2003-2006	470	(27)	2608	(26)	176	(29)	1251	(27)
2007-2010	697	(41)	3330	(33) **	250	(41)	1609	(34) *

[a] Proximal: including the caecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure; Distal: including the descending colon and sigmoid; * $p<0.05$; ** $p<0.0001$.

During the whole study period, almost all patients with stage I to III colon cancer underwent resection of their primary tumour (not shown). Chemotherapy administration significantly increased in stage III colon cancer patients with and without diabetes (from 17% in 1995-1998 to 50% in 2007-2010, 38% to 63%, respectively, p<0.0001). Nevertheless, the utilisation rate of chemotherapy for patients with diabetes remained lower compared to patients without diabetes (Figure 2a). Multivariable logistic regression analysis, including age, gender, specific comorbidities, and period of diagnosis, showed that diabetes was associated with less frequent administration of adjuvant chemotherapy in stage III colon cancer patients (OR 0.7; 95% CI 0.5-0.9; p=0.002). We observed no statistically significant interaction between diabetes and age, gender, and any of the specific comorbidities in stage III colon cancer patients who received chemotherapy. In metastatic colon cancer patients with and without diabetes administration of chemotherapy increased significantly, while the resection rate decreased (Figure 2b and c).

Almost all patients with stage I to III rectal cancer underwent resection of their primary tumour (not shown). In rectal cancer patients with T3 and 4 tumours, the application of chemo-radiation increased (Figure 2d). Multivariable logistic regression analysis showed no significant association between diabetes and the rate of chemo-radiation administration (OR 0.8; 95% CI 0.6-1.1) (Table 2). However, there was less administration of chemo-radiation in individuals with diabetes compared to those without (Figure 2d). Administration of radiotherapy strongly increased over time: the proportion of stage II/ III rectal cancer patients with and without diabetes who received radiotherapy was comparable in recent years, 81% and 87%, respectively (Figure 2e). Multivariable regression analyses showed a negative effect of the presence of diabetes on the utilisation rate of radiotherapy in rectal cancer, although this was not significant and depended on the period of diagnosis (Table 2).

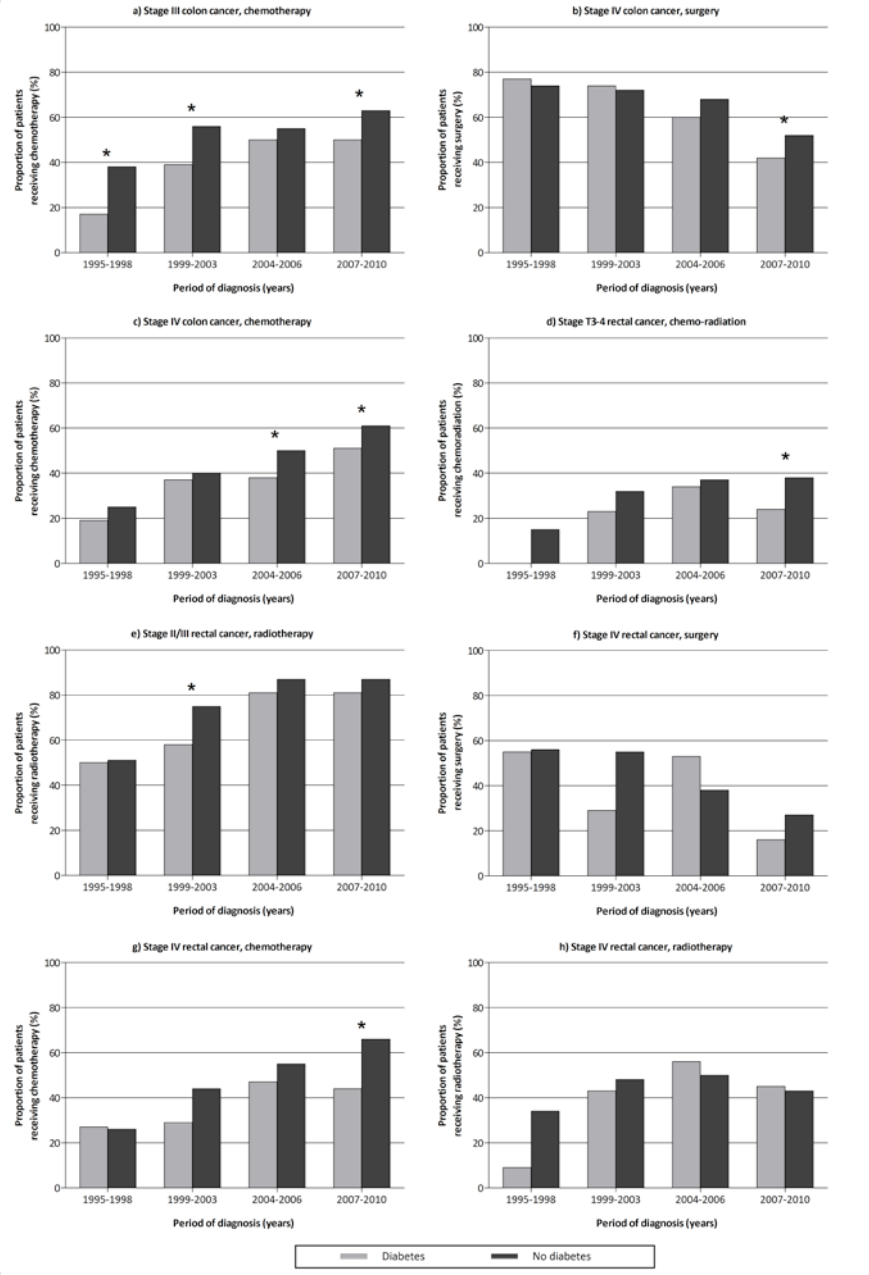
The resection rate decreased over time in rectal cancer patients with metastatic disease, declining from 55% in 1995-1998 to 16% in 2007-2010 in patients with diabetes compared to a decline from 56% to 27% for those without. Furthermore, stage IV rectal cancer patients with diabetes less frequently received chemotherapy and more often received radiotherapy compared to patients without diabetes (Figure 2g and 2h). In the multivariable logistic regression analysis, administration of chemotherapy correlated with both age and cardiovascular disease, while administration of radiotherapy was only associated with the period of diagnosis in stage IV rectal cancer (Table 2).

Table 2. Logistic regression analyses for receiving chemotherapy, chemo-radiation, and radiotherapy in colon and rectal cancer patients (n=17,170).

	Colon cancer						Rectal cancer					
	Chemotherapy		Chemotherapy		Chemo-radiation		Chemotherapy		Radiotherapy		Radiotherapy	
	stage III		stage IV		T3-4		stage IV		stage II/III		stage IV	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
DM												
No	1.0		1.0		1.0		1.0		1.0		1.0	
Yes	0.7	(0.5-0.9) *	0.9	(0.7-1.2)	0.8	(0.6-1.1)	0.7	(0.5-1.2)	0.8	(0.6-1.1)	1.1	(0.7-1.6)
Gender												
Male	1.2	(1.0-1.5) *	1.2	(1.0-1.4)	1.2	(1.0-1.5)	1.1	(0.8-1.4)	0.9	(0.8-1.2)	1.2	(0.9-1.6)
Female	1.0		1.0		1.0		1.0		1.0		1.0	
Period of diagnosis												
1995-1998	1.0		1.0		1.0		1.0		1.0		1.0	
1999-2002	2.8	(2.1-3.7) **	2.2	(1.7-3.1) **	3.1	(1.7-5.5) *	1.9	(1.2-3.1) *	2.7	(2.0-3.5) **	1.8	(1.2-2.4) *
2003-2006	3.8	(2.9-5.1) **	3.6	(2.7-4.8) **	4.3	(2.5-7.4) **	3.8	(2.4-6.0) **	7.0	(5.2-9.4) **	2.1	(1.4-3.2) *
2007-2010	5.2	(4.0-6.8) **	7.1	(5.4-9.5) **	4.3	(2.5-7.4) **	6.8	(4.3-10.8) **	7.0	(5.3-9.3) **	1.6	(1.1-2.4) *
Age at diagnosis (years)												
<49	7.1	(4.3-11.5) **	4.3	(2.9-6.2) **	2.4	(1.6-3.5) **	4.1	(2.2-7.5) **	1.5	(1.0-2.3) *	1.4	(0.9-2.4)
50-64	4.0	(3.2-5.0) **	2.7	(2.2-3.3) **	2.0	(1.6-2.5) **	2.7	(1.9-3.6) **	1.9	(1.5-2.4) **	1.1	(0.8-1.4)
65-79	1.0		1.0		1.0		1.0		1.0		1.0	
80+	<0.1	(<0.1-0.1) **	0.1	(0.1-0.1) **	0.2	(0.1-0.3) **	0.1	(<0.1-0.2) **	0.5	(0.4-0.6) **	0.5	(0.3-0.8) *
Comorbidities (yes vs. no)												
Cardiovascular disease	0.7	(0.6-0.9) *	0.9	(0.7-1.1)	0.7	(0.5-0.9) *	0.6	(0.4-0.9) *	0.8	(0.6-1.0)	1.1	(0.8-1.5)
Hypertension	1.1	(0.9-1.3)	1.0	(0.8-1.2)	1.0	(0.7-1.2)	1.1	(0.8-1.5)	1.2	(0.9-1.5)	1.0	(0.8-1.4)
Previous cancer	0.5	(0.4-0.6) **	0.8	(0.6-1.0)	0.7	(0.5-1.0)	0.7	(0.5-1.1)	0.5	(0.4-0.6) **	0.7	(0.5-1.0)
Pulmonary disease	0.6	(0.5-0.8) *	0.7	(0.5-0.9) *	0.7	(0.5-1.1)	0.9	(0.5-1.4)	1.0	(0.7-1.4)	0.8	(0.5-1.2)
Cerebrovascular disease	0.6	(0.4-0.9) *	0.4	(0.2-0.7) *	0.9	(0.4-1.7)	0.7	(0.4-1.5)	1.0	(0.6-1.5)	0.7	(0.4-1.4)

OR: Odds Ratio; * p<0.05; ** p<0.0001.

Figure 2. Proportion of colon and rectal cancer patients receiving treatment according to the diabetes status.



* Chi square test with p-value < 0.05, tested within subgroup 'period of cancer diagnosis'.

Discussion

In this population-based study covering a period of 16 years and including more than 17,000 CRC patients, we observed substantial changes in the treatment of CRC patients according to their diabetes status. Although CRC patients with diabetes continue to receive chemotherapy less frequently compared to those without, the use of chemotherapy in patients with CRC has increased sharply over time. Furthermore, the proportion of stage II/III rectal cancer patients with and without diabetes who received radiotherapy increased at a similar rate in recent years. Data from recent years show that rectal cancer patients with metastatic disease are more likely to receive radiotherapy when they have diabetes, while patients without diabetes are more likely to receive chemotherapy.

The observed trends in the treatment of colon and rectal cancer found in this study are in line with previous population-based studies. However, these studies did not investigate the potential differences related to diabetes status[9-11]. Our previous study showed similar results[6]. Interestingly, after including the more recent years, CRC patients with diabetes still received chemotherapy less often in the present study. Although the findings of the previous Dutch studies showed that the proportion of patients receiving radiotherapy increased as well, they did not differentiate between patients with and without diabetes[9,11,14,18]. The observation that a similar proportion of patients with and without diabetes received radiotherapy was not seen in previous studies. This could be because earlier studies were based on less recent data.

The prevalence of diabetes in our cohort showed a similar increase to that in the general population, in which the prevalence of diabetes increased from 12% in 2003 to 16% in 2010[19]. This could be explained by the increasing age and life expectancy, as well as the increasing awareness and diagnosis of diabetes. The increase in diabetes prevalence may have led to a growing specific knowledge of CRC care in patients with diabetes. This is reflected by the fact that medical specialists are better in selecting patients who might benefit from a particular treatment. Furthermore, chemotherapy-induced toxicity may be better treated. This knowledge could shift the approach to using more aggressive treatment and multimodal treatment in people with diabetes, as partly confirmed by our data. Several reasons are given in the literature to explain why cancer patients with comorbidity or diabetes receive chemotherapy less frequently, including older age with a shorter life expectancy, decline of adjuvant treatment in the patient, and a higher rate of treatment-related complications. However, it should be noted that studies have shown conflicting results[20-24]. We do not know whether the lower utilisation rate of aggressive therapies in CRC patients with diabetes indicate that

the clinicians appropriately responded to the patients' diminished life expectancy and/or comorbidity or whether this was inappropriate. In view of the growing proportion of CRC patients with diabetes and patients with other comorbidities that are related to changes in lifestyle factors, clinicians will more often face difficult decisions regarding (chemo)therapy.

For stage III colon cancer, administration of chemotherapy is strongly advised because of survival benefits for patients with and without diabetes. However, such evidence concerning chemo-radiation is currently lacking for rectal cancer patients[25,26]. A meta-analysis found no indications of benefit in the four trials where all or at least some of the rectal cancer patients had received preoperative RT or chemo-radiation[26].

Studies in elderly rectal cancer patients and patients with comorbidity showed a good response rate and tolerance to a short pre-operative course of radiotherapy or radiotherapy as sole treatment[27,28]. In recent years, especially in patients with comorbidity, radiotherapy is used as downstaging and not directly followed by surgery. This trend could partially explain the tremendous increase in radiotherapy and the slight increase of chemo-radiation in rectal cancer patients with diabetes. Based on good responses in elderly patients with comorbidity, a discussion was held in our region, after which awareness for the adequate administration of radiotherapy in patients with comorbidity like diabetes increased. The implementation of a new national guideline for radiotherapy in rectal cancer patients in 2001 was even more important for increasing the administration rate of radiotherapy[13,18].

For metastatic colon and rectal cancer, resection rates decreased, while chemotherapy and radiotherapy administration increased. While resection is the only primary curative treatment for CRC in stages I-III CRC, the higher postoperative mortality rate in CRC patients with diabetes in stage IV disease may have led to the decline of surgery over time[20,21,24,27]. Patients with metastatic rectal cancer and diabetes received chemotherapy less often and radiotherapy more often compared to those without diabetes. The national rectal cancer guideline does advise administration of chemotherapy in patients with comorbidity, since chemotherapy does have a survival benefit in these patients[29]. Nevertheless, radiotherapy is not advised, while the ESMO guideline recommends that radiotherapy should be considered as a palliative procedure in selected cases[30]. Consequently, the current study shows that the decision of the medical specialist, which is based on clinical experience, plays a major role in the choice of treatment administration.

The strength of this study is its population-based nature using a quality controlled cancer registry system. However, detailed information on the performance status of the patients, doses and dose adjustments of chemotherapy, and treatment-related complications was not available. Specific information about diabetes (medication, type, duration and severity) was missing, which may have influenced the decision of the clinician. Furthermore, the current study investigated trends in primary treatment in a large region in the Netherlands: therefore, the results could be different from other countries and only concern the primary treatment of a CRC patient.

In conclusion, although this study showed that the proportion of CRC patients with diabetes receiving radiotherapy and chemotherapy increased, patients with diabetes still received chemotherapy less often than those without. Adherence to clinical guidelines is generally considered a measure of quality of care. Deviating from these guidelines in the case of an elderly patient with comorbidity does not necessarily indicate an inferior quality of care. CRC patients with a good health status could benefit from the same treatment chosen for younger patients and extensive treatment of elderly patients with a poor health status should be avoided. In future studies, we will investigate the influence of more aggressive treatment on outcomes in CRC patients with diabetes. In addition, recent linkage of the ECR with pharmacy records from the PHARMO[31] (Institute for Drug Outcomes Research) database will make it possible to investigate the effect of diabetes medication and metabolic control on survival rates in CRC patients.

References

1. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2011;26(11):863-76.
2. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679-87.
3. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.
4. The Netherlands Cancer Registry. www.cijfersoverkanker.nl. accessed on 29-03-2012.
5. Signaleringscommissie Kanker. Cancer in the Netherlands till 2020 [Kanker in Nederland tot 2020, trends en prognoses]. Dutch Cancer Society. 2011.
6. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
7. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol. 2011;30(1):53-9.
8. van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. Diabetologia. 2012;55(8):2163-72.
9. Elferink MA, van Steenbergen LN, Krijnen P, Lemmens VE, Rutten HJ, Marijnen CA, et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989-2006. Eur J Cancer. 2010;46(8):1421-9.
10. van Steenbergen LN, Elferink MA, Krijnen P, Lemmens VE, Siesling S, Rutten HJ, et al. Improved survival of colon cancer due to improved treatment and detection: a nationwide population-based study in The Netherlands 1989-2006. Ann Oncol. 2010;21(11):2206-12.
11. Lemmens V, van Steenbergen L, Janssen-Heijnen M, Martijn H, Rutten H, Coebergh JW. Trends in colorectal cancer in the south of the Netherlands 1975-2007: rectal cancer survival levels with colon cancer survival. Acta Oncol. 2010;49(6):784-96.
12. Brenner H, Bouvier AM, Foschi R, Hackl M, Larsen IK, Lemmens V, et al. Progress in colorectal cancer survival in Europe from the late 1980s to the early 21st century: the EUROCARE study. Int J Cancer. 2011;131(7):1649-58.
13. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638-46.
14. den Dulk M, Krijnen P, Marijnen CA, Rutten HJ, van de Poll-Franse LV, Putter H, et al. Improved overall survival for patients with rectal cancer since 1990: the effects of TME surgery and pre-operative radiotherapy. Eur J Cancer. 2008;44(12):1710-6.
15. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 7th Edition, Wiley Blackwell. 2009.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
17. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. Int J Epidemiol. 1993;22(3):369-76.
18. Jobsen JJ, Aarts MJ, Siesling S, Klaase J, Louwman WJ, Poortmans PM, et al. Use of primary radiotherapy for rectal cancer in the Netherlands between 1997 and 2008: a population-based study. Clin Oncol (R Coll Radiol). 2011;24(1):e1-8.
19. Nivel, LINH-registration general practitioners , http://www.nivel.nl/incidentie-en-prevalentiecijfers-in-de-huisartsenpraktijk, Retrieved 09-08-2012.
20. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol. 2005;55(3):231-40.
21. Lemmens VE, Janssen-Heijnen ML, Verheij CD, Houterman S, Repelaer van Driel OJ, Coebergh JW. Co-morbidity leads to altered treatment and worse survival of elderly patients with colorectal cancer. Br J Surg. 2005;92(5):615-23.

22. Shahir MA, Lemmens VE, van de Poll-Franse LV, Voogd AC, Martijn H, Janssen-Heijnen ML. Elderly patients with rectal cancer have a higher risk of treatment-related complications and a poorer prognosis than younger patients: a population-based study. Eur J Cancer. 2006;42(17):3015-21.

23. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med. 2001;345(15):1091-7.

24. van Waalwijk MA, van de Schans SAM, Haak HR, Extermann M, Dercksen MW, Janssen-Heijnen M. Diabetes alone should not be a reason for withholding adjuvant chemotherapy for stage III colon cancer. Journal of comorbidity. 2011;1:19-27.

25. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109-16.

26. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. Ann Oncol. 2010;21(9):1743-50.

27. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. Lancet Oncol. 2008;9(5):494-501.

28. Vulto AJ, Lemmens VE, Louwman MW, Janssen-Heijnen ML, Poortmans PH, Lybeert ML, et al. The influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. Cancer. 2006;106(12):2734-42.

29. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal Cancer Collaborative Group. BMJ. 2000;321(7260):531-5.

30. Glimelius B, Pahlman L, Cervantes A. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v82-6.

31. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395-404.

5

Exposure to metformin started after colorectal cancer diagnosis and mortality: using a novel approach with time-varying exposure

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Abstract

Background: Several observational studies suggest protective effects of metformin on mortality in patients with diabetes and cancer. Trials on metformin exposure in non-diabetics are developed on the basis of former studies which failed to take cumulative exposure into account. This population-based study aims to assess whether metformin use started *after* colorectal cancer (CRC) diagnosis is associated with overall mortality compared with sulfonylurea derivatives use in diabetics.

Methods: All (n=7,794) primary CRC patients diagnosed between 1998 and 2010 were selected from the Eindhoven Cancer Registry (ECR) and linked to drug dispensing data from the PHARMO Database Network. The association between metformin use started *after* CRC diagnosis and overall mortality, was analysed using Cox regression models with time-varying cumulative drug use.

Results: *After* CRC diagnosis, 164 patients started with metformin monotherapy and 108 patients with sulfonylurea derivatives monotherapy. At the start of glucose lowering drugs, multivariate time-dependent analyses showed that metformin users had a statistically significant lower hazard of overall mortality compared to sulfonylurea derivatives users (HR 0.41; 95% CI 0.21-0.82). However, this survival difference was not associated with the use of the drug, since it seemed to disappear with increasing cumulative exposure to metformin or sulfonylurea derivatives over time ($HR_{drug*cumulative\ exposure}$ 1.03; 95% CI 0.99-1.06; per month; p=0.1).

Conclusions: Cumulative metformin exposure *after* CRC diagnosis is not associated with decreased overall mortality compared with sulfonylurea derivatives exposure. However, at the start of glucose lowering drugs we observed lower overall mortality among metformin users, suggesting that these patients have favourable prognostic factors.

Introduction

Numerous epidemiological studies have shown that colorectal cancer (CRC) occurs more commonly in individuals with type 2 diabetes than in the general population[1-4]. Given the increasing prevalence of both diseases[5-7], even a modest association between these two could have a considerable effect on public health. In addition, in several studies cancer patients with diabetes had a significantly higher overall mortality risk compared with patients without diabetes[8-11].
However, this association seems to vary with glucose lowering drugs, those treated with metformin appear to have decreased overall mortality[9,12-18]. Although these studies adjusted for various important confounders, it is unclear whether the observed decreased mortality found in metformin users could be attributed to the use of metformin before and/or after cancer diagnosis[12,14,16-18]. Furthermore, these studies included metformin use as a dichotomous variable in the analyses[12,14,16-18]. Since the medication use of an individual with diabetes is highly variable over time, including cumulative exposure in the analyses is a more accurate method to investigate the effect of metformin on mortality[19]. Also, previous studies might have overestimated the protective effect of metformin due to biases such as immortal time bias[20], since they classified the exposure time between CRC diagnosis and the first dispensing of metformin as exposed while this should be analysed as unexposed.

As a consequence of methodological limitations in previous observational studies, the debate on whether metformin might be a candidate drug as anti-tumor agent is ongoing. The aim of this study was to assess whether, and to which extent, cumulative use of metformin started *after* the diagnosis of CRC is associated with decreased overall mortality compared with cumulative use of sulfonylurea derivatives. To reduce confounding by indication we compare metformin users with sulfonylurea derivative users, both drugs are the most frequently used first choice drugs at diabetes diagnosis. We hypothesise that overall mortality will decrease with increasing cumulative exposure to metformin in comparison with sulfonylurea derivatives.

Methods

Data sources

Data were obtained from the Eindhoven Cancer Registry (ECR) and linked on a patient level to the PHARMO Database Network covering a demographic region in the South-Eastern part of the Netherlands of approximately one million inhabitants. The construct and validity of the ECR-PHARMO cohort have been described elsewhere[21].
The ECR, maintained by the Netherlands Comprehensive Cancer Organisation

(IKNL), records data on all patients newly diagnosed with cancer in the South-eastern part of the Netherlands, an area with 2.4 million inhabitants. The registry is notified by ten community hospitals, six pathology and two radiotherapy departments. Trained registration clerks actively collect data on diagnosis, patient characteristics, staging, and initial treatment from hospital medical records.
The PHARMO Database Network is a large, patient-centric data network including linked observational databases designed for safety and outcomes research of drugs. For this study the community pharmacy (out-patient) database was used, which includes data on dispensed drug, dispensing date, prescribed dose regimens, and duration of use. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification[22]. Both the ECR and the PHARMO Database Network are recognised as high quality sources for epidemiological research that collect information in overlapping regions in the Netherlands for a period of at least 10 years[21].

Study population

The source population included all CRC patients registered in the ECR-PHARMO cohort between January 1, 1998 and December 31, 2010. Patients with unknown tumour site within the colorectum (C 18.8-18.9) or unknown TNM stage were excluded.
From this source population patients using any type of glucose lowering drug (ATC code: A10) *after* CRC diagnosis were selected. To ensure a study cohort of incident glucose lowering drug users, patients needed to have a six month period without dispensing of any diabetes drug before CRC diagnosis. Patients who started using metformin (ATC-code : A10BA02) or sulfonylurea derivatives (ATC-code : A10BB) were selected. Sulfonylurea derivatives users are the most straightforward comparators of metformin users. CRC patients who used metformin or sulfonylurea derivatives at the time of the first drug dispensing in combination with another glucose lowering drug were excluded (e.g. thiazolidinediones or insulin).

Exposure and outcome

The cumulative days of exposure for metformin and sulfonylurea derivatives at any point in time during follow-up were calculated for each patient in days since the start of the respective glucose lowering drug. This cumulative exposure was determined from this time point until death, loss to follow-up, start of another drug, or end of study period at 31 October 2011, whichever occurred first. Our outcome measure was overall mortality, which was obtained from the municipal personal records database.

Covariates

Age at first glucose lowering drug dispensing, sex, time between CRC diagnosis and first drug dispensing, calendar year of first dispensing, stage of cancer, type of CRC, administration of surgery, radiotherapy and/or chemotherapy and co-medication (lipid modifying agents (ATC-code : C10) and platelet aggregation inhibitors (ATC-code : B01AC)[22]) were considered potential confounders. These covariates, determined at cohort entry, were included in the multivariate analyses as time-fixed variables. The use of co-medication was defined as use somewhere in the first six months after the first dispensing of glucose lowering drugs.

Statistical analysis

Differences in patient characteristics between metformin and sulfonylurea derivatives users were analysed using chi square and the independent samples t-test. To illustrate the prognostic effect of baseline differences between the two groups, the crude overall survival of CRC patients starting on metformin or sulfonylurea derivatives was illustrated with a Kaplan-Meier curve. Multivariable Cox proportional hazards models were analysed, with duration of cumulative drug use as time-varying determinant, as described earlier[19]. This model included a dichotomous variable of the drug (metformin vs. sulfonylurea derivatives) and a continuous time-dependent variable on cumulative exposure per month to either metformin or sulfonylurea derivatives. To assess whether the baseline difference, which was assessed with the dichotomous variable, changed with cumulative drug exposure, an interaction term combining the two was included. This interaction term is the variable we are interested in, since it reflects the effect of the drug metformin (over time), while this variable is fully adjusted for differences at baseline and as a result not influenced by potential confounding by indication. The change with cumulative drug exposure was evaluated and illustrated by calculating hazard ratios at baseline, and after 6, 12, 18, 24, 30 and 36 months of cumulative exposure to the drugs.

Proportionality of the time-dependent Cox model was assessed by including an interaction term with the log of survival, the dichotomous variable of the drug and the continuous time-dependent variable time. A p-value <0.05 was considered statistically significant. Analyses were performed using SAS software (version 9.2, SAS institute, Cary, US).

Subgroup- and sensitivity analyses

Colon and rectal cancer patients as well as patients receiving chemotherapy and/or radiotherapy were analysed in subgroup-analyses. In another subgroup-analysis CRC patients with stage IV disease were excluded, since these patients have a worse prognosis and could have influenced the results strongly. The effect of dose of metformin and sulfonylurea derivatives exposure was assessed in additional stratified analyses, in which patients starting on a high dose of metformin (DDD>0.25) and sulfonylurea derivatives (DDD>0.67) were compared and those starting on a low dose of metformin (DDD≤0.25) and sulfonylurea derivatives (DDD≤0.67) were compared.

To evaluate the robustness of our findings, an 'intention to treat' analysis was performed in which patients who switched or received an additional drug after the drug of the first dispensing were not censored. In another sensitivity analysis CRC patients who only had two or fewer drug dispensings were excluded, to eliminate the effect of transient diabetes cases. The Medication Possession Ratio (MPR) was used as indicator for medication adherence during follow-up and was calculated for each patient by dividing the cumulative days of drug exposure by the total follow-up[23]. A result of ≥ 80% was regarded as adherent to the specific drug. A sub-analysis was performed in which patients not adherent to diabetes treatment (MPR < 80%) were excluded.

Results

Within the ECR-PHARMO cohort, out of 7,794 CRC patients diagnosed between 1998 and 2010, 337 patients who started using glucose lowering drugs *after* CRC diagnosis were selected (Figure 1). Of this cohort 164 patients started with metformin monotherapy and 108 patients started with sulfonylurea derivatives monotherapy after CRC diagnosis. Other CRC patients with diabetes, excluded in this study, started with monotherapy insulin (n=43), combination treatment with metformin and sulfonylurea derivatives (n=13), or another combination treatment (n=9). Among CRC patients starting on metformin or sulfonylurea derivatives the age and sex ratio were approximately similar, while those who used metformin started in more recent years (p<0.0001) (Table 1). In addition, metformin users were more often prescribed lipid modifying agents compared to sulfonylurea derivatives (55% vs. 31%; p<0.0001). The duration of follow-up and the duration of drug exposure was not significantly different between the two groups, although metformin users were more often adherent to drug treatment compared to sulfonylurea derivatives users (80% vs. 65%; p=0.006). Regarding characteristics of CRC, the time between the diagnosis of CRC and the first dispensing of glucose lowering drugs was significantly longer for patients using metformin compared to those using sulfonylurea derivatives (2.5 years vs. 1.1 years; p<0.0001).

Figure 1. Flowchart of patients selected for analysis.

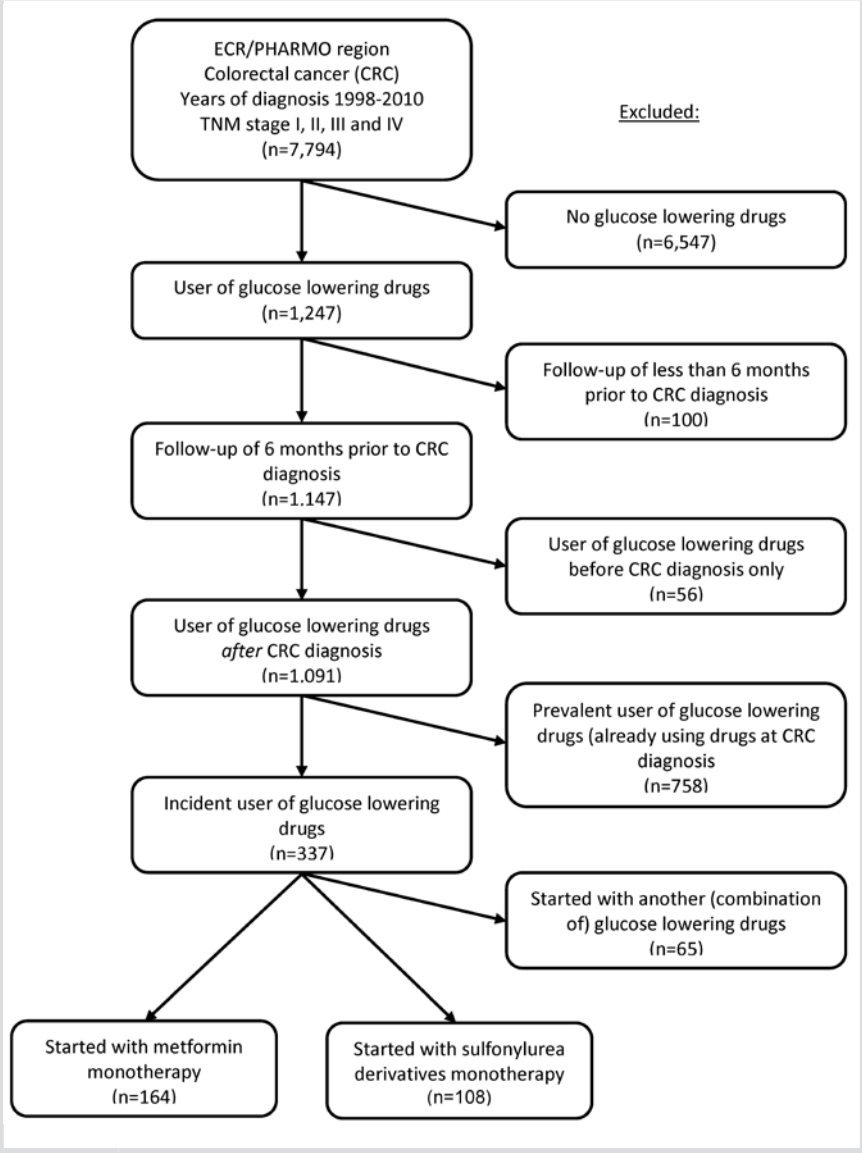
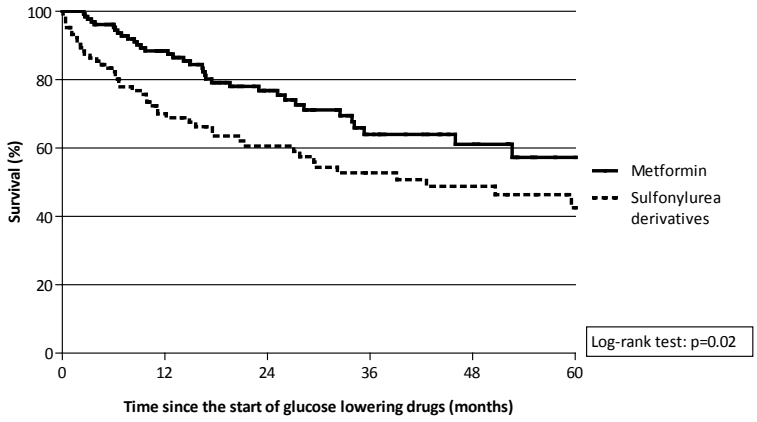


Table 1. Characteristics of patients with colorectal cancer (n=272).

	Metformin		Sulfonylurea derivatives		
	n	(%)	n	(%)	p-value
Characteristics at cohort entry					
Age at first dispensing (years; mean, SD)	71	(±9.4)	72	(±9.9)	0.6
Sex					
Male	93	(57)	61	(56)	
Female	71	(43)	47	(44)	1.0
Period of first dispensing (years)					
1998-2001	3	(2)	18	(17)	
2002-2005	29	(18)	47	(43)	
2006-2008	68	(41)	27	(25)	
2009-2011	64	(39)	16	(15)	<0.0001
Other medication[a]					
Lipid modifying agents (ATC-code : C10)	90	(55)	33	(31)	<0.0001
Platelet aggregation inhibitors (ATC-code : B01AC)	52	(32)	29	(27)	0.4
Follow-up					
Duration of follow-up (years; median, IQR)	1.2	(0.3-2.7)	1.2	(0.5-3.1)	0.2
Duration of drug exposure (years; median, IQR)	0.9	(0.2-2.2)	0.7	(0.1-2.3)	0.3
Patients adherent to medication (> 80% MPR)[b]	131	(80)	70	(65)	0.006
End of follow-up (%)					
Dead	39	(23)	48	(44)	
Censored[c]	56	(34)	39	(36)	
Loss to follow-up	9	(6)	1	(1)	
End of study (31-10-2011)	60	(37)	20	(19)	<0.0001
Characteristics at CRC diagnosis					
Time since CRC diagnosis (years; median, IQR)	2.5	(1.1-5.0)	1.1	(0.4-2.8)	<0.0001
Type of colorectal cancer					
Proximal colon	40	(24)	39	(36)	
Distal colon	58	(36)	38	(35)	
Rectum	66	(40)	31	(29)	0.06
Stage					
I	44	(27)	25	(23)	
II	60	(37)	39	(36)	
III	43	(26)	24	(22)	
IV	17	(10)	20	(19)	0.3
Therapy					
Surgery	157	(96)	105	(97)	0.5
Radiotherapy	45	(27)	20	(19)	0.09
Chemotherapy	39	(24)	32	(30)	0.3

[a] The use of lipid modifying agents or platelet aggregation inhibitors was defined as the use of this co-medication somewhere in the first 6 months after cohort entry; [b] MPR: Medication Possession Ratio, calculated for each patient by dividing the cumulative days of drug exposure by the total follow-up. A MPR of 80% or more was regarded as adherent to the specific diabetes drug; [c] Patients were censored at time of start of another diabetes drug than the drug of the first dispensing.

Figure 2. Kaplan-Meier curve of CRC patients exposed to metformin or sulfonylurea derivatives (n=272) after CRC diagnosis.



Number at risk

Metformin	164	94	60	32	21	10
Sulfonylurea derivatives	108	60	40	29	20	11

5

Overall mortality

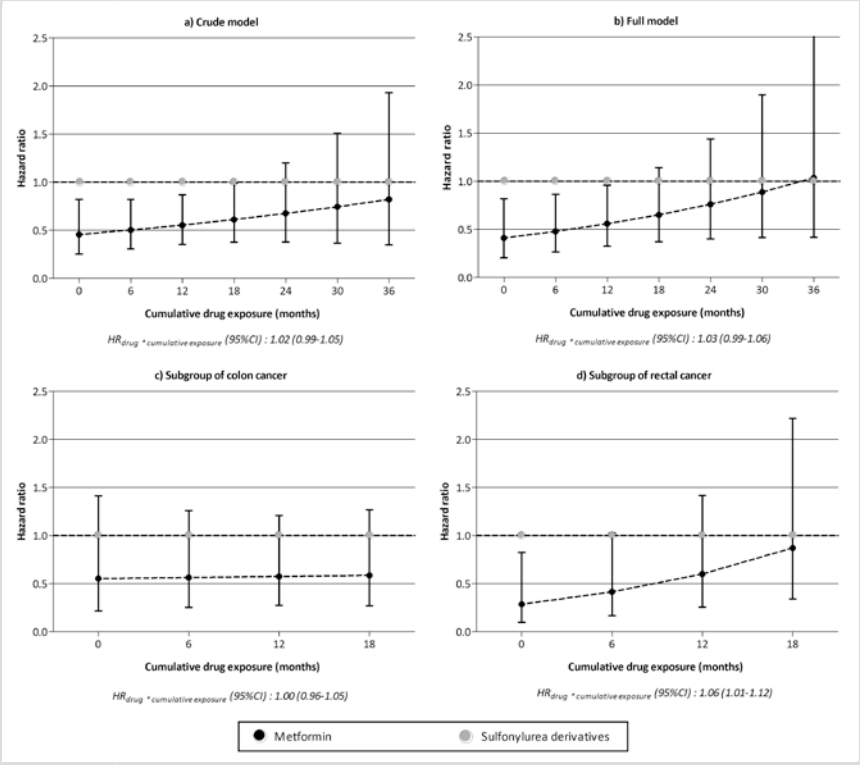
CRC patients who started with metformin *after* CRC diagnosis had lower overall mortality at the moment of start of glucose lowering drugs compared to those who started on sulfonylurea derivatives (log-rank test: p=0.02) (Figure 2). Since this method does not accurately estimate the effect of exposure to metformin and is subject to survivorship selection, time dependent analyses were performed including cumulative exposure to both drugs (Figure 3 and Table 2). The crude time-dependent analyses revealed a difference at the start of glucose lowering drugs (i.e. cumulative exposure = 0) of overall mortality in favour of metformin compared to sulfonylurea derivatives (HR_{drug} 0.46; 95% CI 0.25-0.82) (Figure 3a). This favourable effect in metformin users seemed to disappear with cumulative drug exposure ($HR_{drug*cumulative\ exposure}$ 1.02; 95% CI 0.99-1.05; per month). In the full model, adjusting for time between CRC diagnosis and start of glucose lowering drugs as well as other patient-, tumour-, and co-medication-related variables, the difference in overall mortality between users of metformin and sulfonylurea derivatives at baseline remained significant (HR_{drug} 0.41; 95% CI 0.21-0.82) (Figure 3b). The baseline hazard ratio did change with cumulative drug exposure in favour of sulfonylurea derivates, although this was not significant ($HR_{drug*cumulative\ exposure}$ 1.03; 95% CI 0.99-1.06; per month). After 18 months of drug exposure, CRC

Table 2. Hazard Ratio's comparing overall mortality of CRC patients starting on metformin (n=164) or CRC patients starting on sulfonylurea derivatives (n=108).

	Metformin		Sulfonylurea derivatives		Drug use (Metformin (1) /SU (0))		Cumulative exposure (per month)		Drug*cumulative exposure (per month)	
	Deaths/ n	IR [a]	Deaths/ n	IR [a]	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Main analyses										
Crude	39/164	13.4	48/108	20.7	0.46	(0.25-0.82) *	1.00	(0.97-1.03)	1.02	(0.99-1.05)
Full model	39/164	13.4	48/108	20.7	0.41	(0.21-0.82) *	1.00	(0.96-1.03)	1.03	(0.99-1.06)
Subgroup-analyses										
Colon cancer	19/98	11.0	28/77	16.2	0.55	(0.22-1.41)	1.02	(0.98-1.06)	1.00	(0.96-1.05)
Rectal cancer	20/66	16.9	20/31	34.2	0.29	(0.10-0.82) *	0.93	(0.85-1.01)	1.06	(1.01-1.12) *
Stage I-III	31/147	11.5	34/88	16.6	0.49	(0.22-1.06)	0.99	(0.95-1.02)	1.02	(0.99-1.06)
Chemotherapy	8/39	13.9	18/32	39.0	0.06	(0.01-0.38) *	0.93	(0.85-1.02)	1.13	(1.03-1.24) *
Radiotherapy	12/45	14.0	13/20	38.6	0.05	(0.01-0.39) *	0.89	(0.81-0.97) *	1.03	(0.96-1.11)
Low dose glucose lowering drugs [b]	22/94	11.9	25/54	20.3	0.58	(0.22-1.53)	1.01	(0.97-1.05)	1.00	(0.96-1.05)
High dose glucose lowering drugs [b]	17/70	15.9	23/54	21.2	0.23	(0.08-0.70) *	0.95	(0.89-1.02)	1.09	(1.01-1.16) *
Sensitivity analyses										
Intention to treat	50/164	11.1	63/108	16.5	0.44	(0.24-0.82) *	0.96	(0.94-0.97) **	1.03	(1.00-1.05)
> 2 dispensings	39/130	14.2	39/85	23.3	0.44	(0.21-0.90) *	0.97	(0.93-1.02)	1.03	(1.00-1.07)
Adherent patients [c]	30/131	14.2	30/70	26.2	0.37	(0.16-0.86) *	0.89	(0.73-1.10)	1.02	(0.98-1.07)

SU= sulfonylurea derivatives; All adjusted for age, time since diagnosis, calendar year, stage, surgery, radiotherapy, chemotherapy, type of tumour, and statin and aspirin use within the first 6 months after starting with metformin or sulfonylurea derivatives, except for the crude main analyses; [a] IR: Incidence rate / 100 patient years; [b] In subgroup-analyses with low dose glucose lowering drugs patients starting on a low dose of metformin (DDD≤0.25) and sulfonylurea derivatives (DDD≤0.67) were compared. In subgroup-analyses with high dose glucose lowering drugs patients starting on a high dose of metformin (DDD>0.25) and sulfonylurea derivatives (DDD>0.67) were compared 22; [c] Adherent patients were defined as CRC patients with a Medication Possession Ratio (MPR) of 80% or more. The MPR was calculated for each patient by dividing the cumulative days of drug exposure by the total follow-up; * p<0.05; ** p<0.0001.

Figure 3. Hazard Ratio's of overall mortality of CRC patients starting on metformin (n=164) compared with starting on sulfonylurea derivatives (n=108) according to cumulative drug exposure in months.
a) Crude model; b) Full model, adjusted for age, time between CRC diagnosis and start of glucose lowering drugs, calendar year, stage, surgery, radiotherapy, chemotherapy, type of tumour, and statin and aspirin use within the first 6 months after starting with metformin or sulfonylurea derivatives; c) Subgroup analysis among colon cancer patients (n=175), adjusted for similar variables as the full model; d) Subgroup analysis among rectal cancer patients (n=97), adjusted for similar variables as the full model.



patients started on metformin did not have a significantly lower overall mortality anymore (HR_{drug} at 18 months 0.65; 95% CI 0.37-1.14) (Figure 3b). In the full model proportionality of the time-dependent Cox model was assessed by including an interaction with time and it was not significant (p=0.9).
Subgroup analyses among colon cancer patients (n=177) showed no difference in hazard ratio between metformin and sulfonylurea derivatives users at the start of glucose lowering drugs, while in rectal cancer patients (n=97) it did show a

difference in mortality (HR_{drug} 0.29; 95% CI 0.10-0.82) (Figure 3d). However, in this group of patients the lower mortality in metformin users disappeared with increased cumulative exposure to metformin or sulfonylurea derivatives ($HR_{drug*cumulative\ exposure}$ 1.06; 95% CI 1.01-1.12; per month) (Figure 3d). Similar results were observed for CRC patients with stage I-III disease (n=235) or those who received chemotherapy (n=71) or radiotherapy (n=65) (Table 2).
When the effect of dose was evaluated, the favourable mortality for metformin users compared to that of sulfonylurea derivatives users at the start of glucose lowering drugs was absent in patients with a low first dose (HR_{drug} 0.96; 95% CI 0.59-1.59) and statistically significant in patients with a high first dose (HR_{drug} 0.34; 95% CI 0.14-0.81). However, in those patients using a high first dose the lower mortality for metformin users disappeared with increasing cumulative exposure ($HR_{drug*cumulative\ exposure}$ 1.09; 95% CI 1.01-1.16; per month) (Table 2).

The 'intention to treat' analysis showed comparable results as the full model with at baseline a difference in overall mortality in favour of metformin (HR_{drug} 0.44; 95% CI 0.24-0.82), that did not significantly change with duration of exposure ($HR_{drug*cumulative\ exposure}$ 1.03; 95% CI 1.00-1.05; per month). Sensitivity analyses excluding CRC patients who only had two or fewer drug dispensings (n=55), or sensitivity analysis with patients adherent to diabetes treatment (MPR ≥80%) we observed comparable HRs with that of the full model as well (Table 2).

Discussion

This study, using a time-dependent Cox regression model, showed that cumulative exposure to metformin after CRC diagnosis was not associated with decreased overall mortality compared with cumulative exposure to sulfonylurea derivatives. However, at the start of glucose lowering drugs CRC patients using metformin did have a 59% lower hazard for overall mortality, compared to those starting with sulfonylurea derivatives. In contrast to many recently reported studies[12,14,16-18] that have suggested a beneficial effect of metformin on cancer prognosis, our findings suggest that this survival benefit was not induced by the drug, but was likely confounded by favourable prognostic factors of CRC patients using metformin, for which we could not adjust.

The association between metformin and mortality is extremely complex, since many underlying factors, such as metabolic and lifestyle factors, could be associated with both the exposure to metformin as well as with the outcome. Previous studies regarding metformin and mortality after CRC included dichotomized drug exposure in the analyses as using/non-using a drug[12,14,16-18], whereas the effect of exposure will depend on dose, duration of use, timing in

relationship to the event, concurrent medication, and adherence to therapy[19]. The evidence reported in these previous studies formed the driving force for the conduct of randomised metformin trials[24,25]. In contrast to other studies we avoided time-related biases by analysing exposure to metformin as a time dependent variable[20]. As it is likely that our analyses showed more accurate results than previous studies in CRC patients[12,14,16-18], our findings should trigger more observational studies that also include both cumulative exposure as well as dichotomous variables[26].

The decision of a clinician to prescribe a certain type of glucose lowering drugs is based on the characteristics of a patient, such as the Body Mass Index (BMI), the HbA_{1c} levels and the presence of contraindications for medication[27]. In an observational study like ours it is therefore likely that the strong survival benefit in metformin users compared to sulfonylurea derivatives users, which was illustrated by the baseline hazard and not by the cumulative exposure hazard, is influenced by confounding by indication[9]. In this setting those patients selected for treatment with metformin may possess favourable characteristics that decrease overall mortality compared with sulfonylurea derivatives. This hypothesis is supported by our study results. This better prognosis of metformin users at baseline could also be influenced by a substantial change in the national guidelines on treating individuals with diabetes with different types of glucose lowering drugs. Before 1999 sulfonylurea derivatives were advised to all patients as first line treatment, while after 1999 they were only advised to patients with a BMI of <27. Metformin was advised as first line treatment for patients with a BMI ≥27 after 1999, and for all patients since 2006[28,29]. Since mortality rates decreased slightly for CRC patients between 1998 and 2010[6], this could have overestimated the protective baseline effect of metformin in our study. Besides, the time between CRC diagnosis and the first dispensing of glucose lowering drugs was longer for metformin users compared with sulfonylurea derivatives users, which resulted in survivorship selection in favour of metformin users for which was attempted to adjust in our analyses. Due to small numbers in this study, matching on the time between cancer diagnosis and the start of glucose lowering drugs was not feasible. Besides, metformin, which is administered to those patients with a high BMI, is associated with weight loss and as a result may translate into improved outcomes[30,31]. While analyses in this study were adjusted for the year of first dispensing, valuable information about BMI and HbA_{1c} was unavailable, therefore the potential effect of metformin on weight loss and levels of HbA_{1c}, and thereby indirectly on mortality, was not taken into account. Although co-medication, like lipid modifying agents or platelet aggregation inhibitors, could play a major role in the association between metformin and mortality[32,33], an important confounding

effect of these drugs on overall mortality when comparing metformin with sulfonylurea derivatives was not shown.

In subgroup analyses, unfortunately with small numbers of patients, the hazard ratio associated with longer duration of exposure was different for the two types of cancer. The effect of metformin did not change with cumulative duration in colon cancer patients, whereas in rectal cancer patients this protective effect diminished strongly. In general, metformin users have higher BMI than sulfonylurea derivatives users users, which is related to the Dutch guidelines[28,29]. A recent study showed that higher BMI before the diagnosis of cancer (mean: 7 years before cancer diagnosis) in rectal cancer patients and not in colon cancer patients was associated with elevated CRC-specific mortality[34]. This finding may relate to an increased risk of local recurrence in obese patients with rectal cancer, resulting in higher mortality over time for the metformin users compared with the sulfonylurea derivatives users. Although we had important tumour information at the time of cancer diagnosis and regarding this did not found important differences between the studied patient groups, in our study we were not able to investigate this properly, since information on the presence of recurrence and the cause of death was missing.

Our study revealed a difference in mortality for metformin users compared to sulfonylurea derivatives users using a high dose of glucose lowering drugs. Since the hazard for drug exposure duration was not in favour of metformin, this does not support the hypothesis of a specific drug effect of metformin on mortality in CRC patients. Though, those patients using a high dose are likely to be different from those using a low dose. First, metformin users with a higher BMI may need a high dose of metformin, besides having more reserves at cancer treatment due to their higher BMI. Second, sulfonylurea derivatives users with a high dose may have an even poorer prognosis as they are likely to have worse glycaemic control and more vascular complications. In our study we were able to include the dose of metformin and sulfonylurea derivatives in our database, though these doses for glucose-lowering are relatively low compared with the doses for anti-cancer activity of metformin in preclinical studies, which seemed to be much higher[35].

In conclusion, findings of this observational study suggest that cumulative exposure to metformin is not associated with decreased overall mortality compared to sulfonylurea derivatives in CRC patients with diabetes. However, patients who started with metformin after the diagnosis of CRC already had a decreased overall mortality hazard at start of glucose lowering drugs compared to those started with sulfonylurea derivatives, suggesting that metformin users have favourable

prognostic factors, for which this study could not adjust.
Even though our study design and type of analyses are most accurate, the number of patients included was relatively small, therefore additional evidence in a greater subset of patients is needed. Nevertheless, this study is in contrast with previous reports on the apparent beneficial effect of metformin on survival and provokes initiation of studies with comparable analyses, including both cumulative exposure as well as dichotomous variables, to better adjust for baseline differences.

References

1. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2011;26(11):863-76.
2. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679-87.
3. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.
4. Johnson JA, Carstensen B, Witte D, Bowker SL, Lipscombe L, Renehan AG. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55(6):1607-18.
5. Sloan FA, Bethel MA, Ruiz D, Shea AM, Feinglos MN. The growing burden of diabetes mellitus in the US elderly population. Arch Intern Med. 2008;168(2):192-9; discussion 9.
6. Cancer in the Netherlands till 2020 (2011) Trends and prognoses. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-00-8.
7. Baan CA, Schoemaker CG, Jacobs-van der Bruggen MAM, Hamberg-van Reenen HH, Verkleij H, Heus S, et al. Diabetes tot 2025; preventie en zorg in samenhang. RIVM-rapport 260322004. 2009.
8. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. Jama. 2008;300(23):2754-64.
9. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-32.
10. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
11. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol. 2011;30(1):53-9.
12. Garrett CR, Hassabo HM, Bhadkamkar NA, Wen S, Baladandayuthapani V, Kee BK, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012;106(8):1374-8.
13. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care. 2010;33(2):322-6.
14. Bo S, Ciccone G, Rosato R, Villois P, Appendino G, Ghigo E, et al. Cancer mortality reduction and metformin: a retrospective cohort study in type 2 diabetic patients. Diabetes Obes Metab. 2012;14(1):23-9.
15. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299-304.
16. Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer. 2011;131(3):752-9.
17. Cossor FI, Adams-Campbell LL, Chlebowski RT, Gunter MJ, Johnson K, Martell RE, et al. Diabetes, metformin use, and colorectal cancer survival in postmenopausal women. Cancer Epidemiol. 2013;37(5):742-9.
18. Spillane S, Bennett K, Sharp L, Barron TI. A cohort study of metformin exposure and survival in patients with stage I-III colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2013;22(8):1364-73.
19. Stricker BH, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. Eur J Epidemiol. 2010;25(4):245-51.
20. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care. 2012;35(12):2665-73.
21. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395-404.
22. World Health Organization. Collaborating Centre for Drug Statistics Methodology - ATC/DDD index. Accessed at www.whocc.no/atc_ddd_index, 2014.

23. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. Med Care. 2008;46(11):1125-33.
24. http://www.clinicaltrials.gov, A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer, NCT01101438.
25. http://www.clinicaltrials.gov, A Trial of Standard Chemotherapy With Metformin (vs Placebo) in Women With Metastatic Breast Cancer, NCT01310231.
26. Zanders MM, Vissers PA, van de Poll-Franse LV. Association between metformin use and mortality in patients with prostate cancer: explained by confounding by indication? J Clin Oncol. 2014;32(7):701.
27. http://www.fk.cvz.nl ; Farmacotherapeutisch Kompas: medisch farmaceutische voorlichting/ uitgave van de Commissie Farmaceutische Hulp van het College voor zorgverzekeringen; Bijgewerkt tot 1 juli 2014; J.R.B.J.Brouwers; ISBN 9789085621096
28. Wiersma TJ, Heine RJ, Rutten GE. [Summary of the practice guideline 'Diabetes mellitus type 2' (first revision) of the Dutch College of General Practitioners]. Ned Tijdschr Geneeskd. 1999;143(33):1688-91.
29. Bouma M, Rutten GE, de Grauw WJ, Wiersma T, Goudswaard AN. [Summary of the practice guideline 'Diabetes mellitus type 2' (second revision) from the Dutch College of General Practitioners]. Ned Tijdschr Geneeskd. 2006;150(41):2251-6.
30. Morgan CL, Jenkins-Jones S, Evans M, Barnett AH, Poole CD, Currie CJ. Weight change in people with type 2 diabetes: secular trends and the impact of alternative antihyperglycaemic drugs. Diabetes Obes Metab. 2012;14(5):424-32.
31. de Fine Olivarius N, Andreasen AH, Siersma V, Richelsen B, Beck-Nielsen H. Changes in patient weight and the impact of antidiabetic therapy during the first 5 years after diagnosis of diabetes mellitus. Diabetologia. 2006;49(9):2058-67.
32. Siddiqui AA, Nazario H, Mahgoub A, Patel M, Cipher D, Spechler SJ. For patients with colorectal cancer, the long-term use of statins is associated with better clinical outcomes. Dig Dis Sci. 2009;54(6):1307-11.
33. Lehman DM, Lorenzo C, Hernandez J, Wang CP. Statin use as a moderator of metformin effect on risk for prostate cancer among type 2 diabetic patients. Diabetes Care. 2012;35(5):1002-7.
34. Campbell PT, Newton CC, Dehal AN, Jacobs EJ, Patel AV, Gapstur SM. Impact of body mass index on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol. 2012;30(1):42-52.
35. Dowling RJ, Niraula S, Stambolic V, Goodwin PJ. Metformin in cancer: translational challenges. J Mol Endocrinol. 2012;48(3):R31-43.

6

Letter to the editor:

Association between metformin use and mortality in prostate cancer patients: Explained by confounding by indication?

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Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol. 2013 Sep 1;31(25):3069-75.

Abstract

Purpose: To evaluate the association between cumulative duration of metformin use after prostate cancer (PC) diagnosis and all-cause and PC-specific mortality among patients with diabetes.

Patients and methods: We used a population-based retrospective cohort design. Data were obtained from several Ontario health care administrative databases. Within a cohort of men older than age 66 years with incident diabetes who subsequently developed PC, we examined the effect of duration of antidiabetic medication exposure after PC diagnosis on all-cause and PC-specific mortality. Crude and adjusted hazard ratios (HRs) were calculated by using a time-varying Cox proportional hazard model to estimate effects.

Results: The cohort consisted of 3,837 patients. Median age at diagnosis of PC was 75 years (interquartile range [IQR], 72 to 79 years). During a median follow-up of 4.64 years (IQR, 2.7 to 7.1 years), 1,343 (35%) died, and 291 patients (7.6%) died as a result of PC. Cumulative duration of metformin treatment after PC diagnosis was associated with a significant decreased risk of PC-specific and all-cause mortality in a dose-dependent fashion. Adjusted HR for PC-specific mortality was 0.76 (95% CI, 0.64 to 0.89) for each additional 6 months of metformin use. The association with all-cause mortality was also significant but declined over time from an HR of 0.76 in the first 6 months to 0.93 between 24 and 30 months. There was no relationship between cumulative use of other antidiabetic drugs and either outcome.

Conclusion: Increased cumulative duration of metformin exposure after PC diagnosis was associated with decreases in both all-cause and PC-specific mortality among diabetic men.

To the editor:

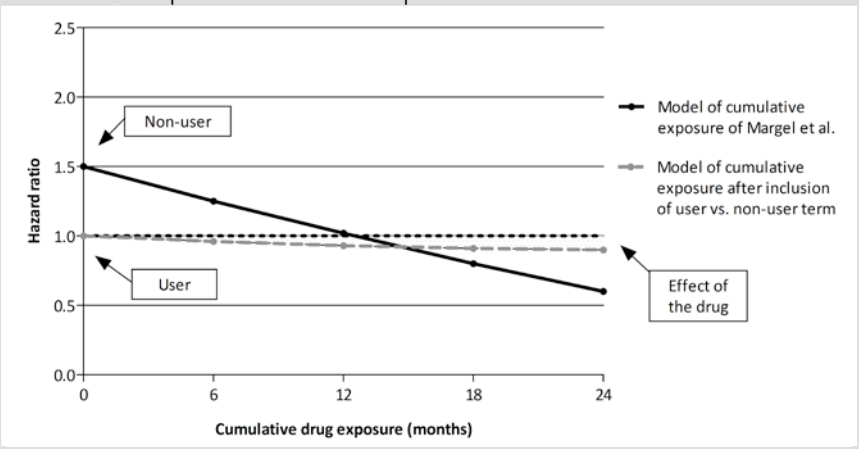
Margel et al.[1] recently reported on a population-based retrospective cohort study that used a unique large database to investigate patients with prostate cancer diagnosed with incident diabetes. Increased cumulative duration of metformin exposure after prostate cancer diagnosis was associated with decreases in both all-cause and prostate cancer-specific mortality among men with diabetes. The study showed that prostate cancer-specific mortality even decreased by 24% for each additional 6 months of metformin use after the diagnosis of prostate cancer. Although the approach used in this study did circumvent numerous potential limitations and biases[2], on the basis of the authors' conclusions and study design, we have a few comments and requests for clarification.

With regard to their statistical analyses, the effects of cumulative duration of exposure to metformin on mortality were assessed by using a Cox proportional hazards model in which drug exposures after prostate cancer diagnosis were modeled as time-dependent covariates. The comparison was not exclusively between users who had different durations of exposure, but also between users and nonusers of the drug. This means that in the time-dependent model, patients not using metformin were included in the analysis as 0 for cumulative use of metformin. Modeling the line for this specific hazard ratio (HR) of cumulative metformin use could be expected to be greatly influenced by events in the nonusers, given that patients using and not using metformin might differ in their previous susceptibility to dying as a result of cancer. As a consequence, these results might be affected by confounding by indication, which could not be avoided by the inclusion of cumulative drug exposure exclusively, as supposed in this analysis.

It can be shown algebraically that with the inclusion of an ever-never term for metformin use in the model, the HR of the cumulative effect term does not depend on the events in the unexposed group and therefore avoids confounding by indication[3] (Figure 1). Thus, we believe it would be essential to include ever-never terms for drug exposure to avoid confounding by indication.

The authors acknowledge that for every additional 6 months of metformin treatment in patients with prostate cancer, there is a significant decrease in all-cause mortality that declines over time. However, the results relating to the postdiagnosis cumulative use of metformin should be interpreted with caution. In the first 6 months after prostate cancer diagnosis an HR of 0.76 for all-cause mortality was shown. Is it biologically plausible that 6 months of metformin use reduces mortality by 24%? In a randomized controlled trial, we would most likely expect an HR of 1 in the first 6 months. To our knowledge, the HR in this study is comparing patients with prostate cancer who used metformin for 6 months with

Figure 1. Schematic figure of the model for cumulative exposure to metformin used by Margel et al.[1] and the model for cumulative exposure that includes a user/nonuser term for metformin, resulting in adjustment for baseline differences between patients with prostate cancer and diabetes who were prescribed metformin compared with those not prescribed metformin.



patients not using metformin at all. As previously mentioned, the 24% decreased hazard of mortality in users compared with nonusers of metformin is the illustration of differences in patients and/or tumor characteristics at baseline. If there is a true dose-response relationship between metformin and mortality, then one would have expected to observe a decline in HR over time (Table 4 in the article by Margel et al.[1]). Instead, for every 6 months after the baseline HR, the mortality in users of metformin is increasing. In our opinion, this should be interpreted as no effect of the drug, but solely confounding by indication.

Despite the fact that the cumulative exposure to metformin was analyzed correctly in the study by Margel et al. [1], their results should be interpreted with caution in light of the initiation of large-scale, long-term randomized trials of metformin in patients with prostate cancer, given that confounding by indication might have occurred.

References

1. Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Metformin Use and All-Cause and Prostate Cancer-Specific Mortality Among Men With Diabetes. J Clin Oncol. 2013;31(25):3069-75.
2. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes care. 2012;35(12):2665-73.
3. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012;55(11):2929-37.

Replies:

- Margel D, Urbach D, Fleshner N, Austin PC. Reply to M.M.J. Zanders et al. J Clin Oncol. 2014;32(7):702.
- Penney KL, Stampfer MJ. Reply to M.M.J. Zanders et al. J Clin Oncol. 2014;32(7):702-3.

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Is there still an effect of metformin, statin and aspirin use on overall mortality among colorectal cancer patients with diabetes if adjusted for one another?

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Abstract

Objective: Use of metformin, statins and aspirin, all individually have been associated with decreased mortality in cancer patients, though, without adjusting for one another. Independent effects of these drugs on overall mortality after colorectal cancer (CRC) diagnosis within glucose lowering drugs (GLDs) users were assessed.

Methods: Patients with primary CRC (1998-2011) were selected from the Eindhoven Cancer Registry (ECR) and linked to drug dispensing data from the PHARMO Database Network. GLDs users before cancer diagnosis were included. The Cox regression model, with CRC diagnosis as baseline, included time-dependent variables of cumulative exposure to metformin, statins and aspirin after cancer diagnosis and time-dependent ever-never terms for drug exposure.

Results: In our study, 1,043 patients used GLDs before CRC diagnosis, of whom 666 (64%) used metformin, 639 (61%) used statins and 490 (47%) used aspirin after CRC diagnosis. Multivariable analyses revealed that longer cumulative exposure to metformin was not associated with overall mortality ($HR_{Cumulative\ exposure\ per\ six\ months}$ 1.02; 95% CI 0.97-1.07), while the favourable effect of statins increased with cumulative drug exposure ($HR_{Cumulative\ exposure\ per\ six\ months}$ 0.93; 95% CI 0.89-0.98). No association between aspirin use and overall mortality was seen ($HR_{Cumulative\ exposure\ per\ six\ months}$ 0.98; 95% CI 0.93-1.03).

Conclusions: This study found no independent association between cumulative exposure to metformin, aspirin and overall mortality, while cumulative exposure to statins after CRC diagnosis was associated with lower overall mortality. Our findings support a drug effect of statins, independent of metformin and aspirin, in CRC patients using GLDs.

Introduction

While individuals with diabetes appear to have a higher overall mortality after CRC, those treated with metformin, a biguanide widely prescribed as first-line glucose lowering drug (GLD), appear to have a decreased overall mortality compared with other diabetes patients[1-7]. In addition, other drugs, such as statins (HMG-CoA reductase inhibitors) and aspirin (acetylsalicylic acid) have also been associated with decreased overall mortality in CRC patients[8-14]. These drugs are frequently prescribed to individuals with diabetes, i.e. around 50% of them use statins and 40% use aspirin according to the current international literature[15-17]. As many diabetes patients use a combination of these three types of drugs, it is justified to wonder if, the suggested association between metformin use and overall mortality among cancer patients is explained by the concomitant use of aspirin or statins, and vice versa[18]. Therefore, the potential individual favourable effect of these drugs should be studied taking into account the effects of the other drugs. A few researchers have followed this approach, adjusting for the effects of other drugs, but always on the basis of dichotomized variables[1,3-6] and never as time-dependent cumulative exposure terms[19]. Those studies reported incredibly low hazard ratios for the individual effects of the drugs among patients with cancer, suggesting strong protective effects. However, an important limitation in these studies was the dichotomisation of use (ever vs. never use) of metformin[1-6], statins[8-10], or aspirin[11-14] in the analyses. Despite the fact that this dichotomous variable will reveal differences in overall mortality between the groups of patients, it will not reveal the effect of the drug over time, since (un)measured differences in prognostic factors will overestimate a potential drug effect[20]. This type of bias in pharmaco-epidemiology, known as allocation bias, has received increasing attention in the field of diabetes and cancer and experts are debating whether the inclusion of the time dependent cumulative exposure is the best option to prevent this bias[19,21].

Thus, the primary objective of this study was to assess the independent effect of metformin, statins and aspirin on overall mortality among CRC patients with diabetes. We hypothesised that overall mortality will decrease with increasing cumulative exposure to metformin, statins and aspirin independently of the effects of the other studied drugs.

Methods

Data sources

Data were obtained from the Eindhoven Cancer Registry (ECR) linked on a patient level to the PHARMO Database Network, covering a demographic region in the Southern part of the Netherlands of approximately one million inhabitants. The

construct and validity of the ECR-PHARMO cohort have been described elsewhere[22]. The ECR, maintained by the Netherlands Comprehensive Cancer Organisation (IKNL), records data on all patients newly diagnosed with cancer in the Southern part of the Netherlands, an area with 2.4 million inhabitants. The registry is notified by six pathology departments, 10 community hospitals, and two radiotherapy departments. Trained registration clerks actively collect data on patient characteristics, cancer diagnosis, staging, and initial treatment from hospital medical records. The PHARMO Database Network is a large, patient-centric data network including multiple linked observational databases designed for safety and outcomes research of drugs. For this study the community pharmacy (out-patient) database was used, which includes data on the dispensed drug, dispensing date, amount and regiment dispensed, and thus the duration of use. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification[23]. Both the ECR and the PHARMO Database Network are recognised as high quality sources for epidemiological research that collect information in overlapping regions in the Netherlands for a period of at least 10 years[22].

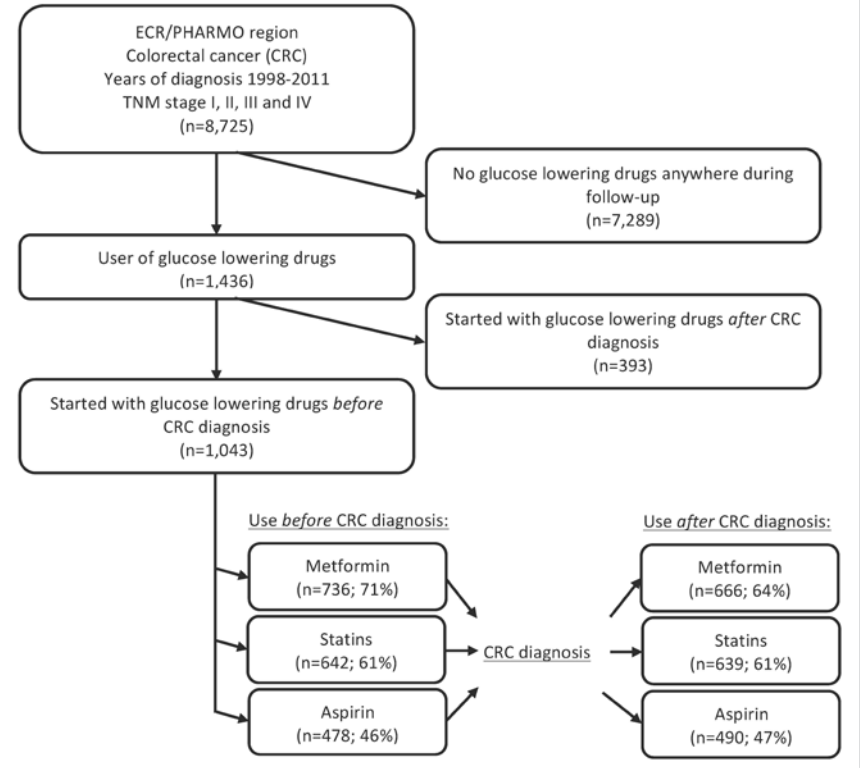
Study population

The source population included all CRC patients registered in the ECR-PHARMO cohort between January 1, 1998 and December 31, 2011 (n=8,725) (Figure 1). From this source population patients using any type of GLD (ATC code: A10) before CRC diagnosis were selected (n=1,043). In this study GLD use was used as a proxy for diabetes onset. In individuals who used GLD before CRC diagnosis, the use of metformin (ATC-code: A10BA02), statins (ATC-code: C10AA, C10BA and C10BX) and low dose aspirin (ATC-code: B01AC06, B01AC08 and B01AC30; ≤100 mg daily) was evaluated. Since we expected that the effect of the drugs on mortality was not different for incident (i.e. started with GLD after entrance in the ECR-PHARMO cohort, thus known diabetes duration; n=607) compared to prevalent (i.e. started with GLD at any time before entrance in the ECR-PHARMO cohort, thus unknown diabetes duration; n=436) users, we decided to include both types of users and performed a sensitivity analyses for incident users.

Exposure and outcome

For each CRC patient, the number of cumulative days of metformin, statins and aspirin exposure *before* (for incident drug users) and *after* CRC diagnosis was calculated. The cumulative days of drug exposure *after* CRC diagnosis were determined from CRC diagnosis until death of the patient, leaving the ECR-PHARMO area, or end of the study period at 31 December 2011, whichever occurred first. The Medication Possession Ratio (MPR) was used as indicator for medication adherence (MPR ≥80%) during follow-up and was calculated by

Figure 1. Flowchart of patients selected for analysis.



dividing the cumulative days of drug exposure by the days of follow-up after CRC diagnosis for that specific patient[24]. The outcome measure for the current study was overall mortality, which was obtained from the municipal personal records database.

Statistical analyses

The association of the effect of metformin, statins and aspirin on overall mortality after CRC diagnosis was analysed using a time-dependent multivariable Cox proportional hazards model, which included all studied drugs. Time since the diagnosis of CRC was used as the underlying timescale in the time-dependent Cox proportional hazard model, thus baseline refers to cancer diagnosis. The use of metformin, aspirin and statins *before* CRC diagnosis was included as ever-never (1 vs. 0) terms in the model, while the cumulative days of drug use *after* CRC diagnosis were included as time-dependent determinants. Since this study included users with different durations of exposure, as well as nonusers of the

drugs, the inclusion of cumulative drug exposure alone might not be sufficient. The events for overall mortality for non-users will all be clustered at the cumulative exposure of zero months having a great impact on modelling the overall hazard ratio for cumulative exposure. It is hypothesised that this will introduce allocation bias, which we tried to avoid by including time-dependent ever-never terms for drug use after CRC diagnosis[20]. The change in overall mortality risk with cumulative drug exposure to either metformin, statins or aspirin was evaluated and illustrated by calculating hazard ratios at baseline, and after 6, 12, 18, 24, 30 and 36 months of cumulative exposure to the drugs.

Since our cohort includes patients with diabetes, we need to account for the use of other GLDs before and after cancer diagnosis: sulfonylurea derivatives (ATC-code: A10BB), insulin (ATC-code: A10A) and other GLDs. The cumulative exposures and ever-never terms of these drugs were included in the multivariable model using a similar approach as for the other drugs. Age at CRC diagnosis, sex, calendar year of CRC diagnosis (year of baseline), stage of cancer, CRC subsite (proximal colon, distal colon or rectal), administration of surgery, radiotherapy and/or chemotherapy were considered potential confounders. These covariates, determined at baseline, were included in the multivariable analyses as time-fixed variables. The presence of effect modification between metformin, statin and aspirin use was evaluated by including interaction terms in our full model (cumulative exposure of studied drug * ever-never term of potential effect modifying drug). A two-sided p-value <0.05 was considered statistically significant. Analyses were performed using SAS software (version 9.3, SAS institute, Cary, US).

Subgroup- and sensitivity analyses

Cancer subsite (colon or rectal) as well as cancer treatment were evaluated as effect modifiers of the drugs under study. To determine whether our results were biased by the inclusion of prevalent users (i.e. users with unknown duration) the prevalent users of either metformin, statins or aspirin were excluded in an additional analysis. To evaluate the effect of metformin, statins and aspirin on long term survival, patients who died in the six months after CRC diagnosis and those without complete follow-up for these six months were excluded in another sensitivity analysis. Since many of the patients in this study used diuretics, beta blocking agents and renin-angiotensin system agents, a further sensitivity analysis was included in which we adjusted for the use of these drugs by including cumulative exposures and ever-never terms.

CRC patients being less adherent might be different from those being more adherent to drugs, to adjust for this, variables for drug adherence (0 = no drug use; 1 = MPR ≥80%; 2 = MPR <80%) for all studied drugs were added to the full

model in another sensitivity analysis.
Since especially the effect of statin use on survival might be confounded by sick stopper (lower adherence among groups with the highest risk of poor outcomes) or healthy user bias (selection of statin users who are more health-conscious)[25], which as a result might have overestimated the effect of statins, we assessed the accuracy of our analyses by performing another sensitivity analysis. The cumulative exposure to statins was adjusted when patients were exposed to statins within the six months prior to their death. The total period of these six months prior to their death, either exposed or unexposed, was then included in this sensitivity model as time exposed to statins.

Results

The study population consisted of 1,043 patients who used GLDs before their diagnosis of CRC (Table 1), of whom 666 (64%) used metformin, 639 (61%) used statins and 490 (47%) used aspirin *after* CRC diagnosis (Figure 1 and Table 1). Most patients had an unknown duration of GLD use since they were prevalent users when entering the database (42%), whereas 32% of the patients in the total cohort had a duration of GLD use which was ≥3 years at the time of CRC diagnosis. During a mean follow-up of 3.4 years (SD ± 3.0), 494 patients (47%) died and 11 (1%) were loss to follow-up before the end of the study, fewer deaths occurred in the groups which used one of the studied drugs (Metformin p<0.0001; Statins p<0.0001; Aspirin p=0.09; Appendix 1).

After the diagnosis of CRC, the median duration of metformin use was 1.6 years (Interquartile range (IQR) 0.5-3.3), for statins this was 2.0 years (IQR 0.6-3.9) and for aspirin this was 1.5 years (IQR 0.2-3.4), with a proportion of adherent users (MPR ≥ 80%) for all drugs of around 50%. Of the total study cohort, 25% of the patients used all drugs under study, while 15% of the patients used none of them after CRC diagnosis (Appendix 1). Many CRC patients used other drugs after the diagnosis of cancer (mean follow-up 3.4 ± 3.0 years), 58% used sulfonylurea derivatives, 47% diuretics, 45% beta blocking agents and 53% renin-angiotensin system agents. Metformin, statin and aspirin users, used significantly more beta blocking agents and renin-angiotensin system agents compared to those not using the studied drugs (Appendix 1). Although the characteristics of CRC were comparable for the different drug groups according to Table 1, the proportion of statin users with rectal cancer was higher (33% versus 24%; p=0.005), while the proportion of statin users with stage IV disease was lower (16% vs 22%; p<0.0001) compared to those not using statin during follow-up (Appendix 1).

Table 1. Baseline characteristics of the study population according to medication use after CRC diagnosis (n=1,043).

	Total		Metformin users (n=666)		Statin users (n=639)		Aspirin users (n=490)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients	1043	(100)	666	(64)	639	(61)	490	(47)
Age at CRC diagnosis (years; means (SD))	73.2	(± 9.1)	72.3	(± 8.8)	71.9	(± 8.5)	73.5	(± 8.8)
Male	543	(52)	366	(55)	377	(59)	284	(58)
Duration of GLD use at CRC diagnosis								
< 1 years	108	(10)	74	(11)	63	(10)	50	(10)
1 – 3 years	168	(16)	110	(16)	103	(16)	68	(14)
≥ 3 years	331	(32)	225	(34)	206	(32)	153	(31)
Prevalent user	436	(42)	257	(39)	267	(42)	219	(45)
Duration of follow-up (years; means (SD))	3.4	(± 3.0)	3.7	(± 3.0)	3.8	(± 3.0)	3.9	(± 3.2)
End of follow-up								
Death	494	(47)	272	(41)	223	(35)	219	(45)
Loss to follow-up	11	(1)	7	(1)	7	(1)	3	(1)
End of study (31-12-2011)	538	(52)	387	(58)	409	(64)	268	(54)
Use of the drugs under study after CRC diagnosis								
Metformin	666	(64)	666	(100)	469	(73)	336	(69)
Duration of metformin use (years; median (IQR))	1.6	(0.5-3.3)	1.6	(0.5-3.3)	1.9	(0.7-3.6)	1.9	(0.6-3.6)
Adherent users (MPR ≥ 80%) [a]	364	(55)	364	(55)	260	(55)	178	(53)
Statins	639	(61)	469	(70)	639	(100)	359	(73)
Duration of statin use (years; median (IQR))	2.0	(0.6-3.9)	2.2	(0.8-4.1)	2.0	(0.6-3.9)	2.2	(0.7-4.2)
Adherent users (MPR ≥ 80%) [a]	362	(57)	276	(59)	362	(57)	208	(58)
Aspirin	490	(47)	336	(51)	359	(56)	490	(100)
Duration of aspirin use (years; median (IQR))	1.5	(0.2-3.4)	1.6	(0.2-3.5)	1.7	(0.2-3.6)	1.5	(0.2-3.4)
Adherent users (MPR ≥ 80%) [a]	235	(48)	167	(50)	174	(48)	235	(48)
Use of the drugs under study before CRC diagnosis								
Metformin	736	(71)	591	(89)	480	(75)	336	(69)
Prevalent user (% of metformin use)	158	(21)	128	(22)	103	(21)	80	(24)
Statins	642	(61)	437	(66)	556	(87)	342	(70)
Prevalent user (% of statin use)	182	(28)	111	(25)	164	(29)	111	(32)
Aspirin	478	(46)	305	(46)	326	(51)	386	(79)
Prevalent user (% of aspirin use)	189	(40)	108	(35)	131	(39)	156	(40)

[a] MPR: Medication Possession Ratio, calculated for each patient by dividing the cumulative days of drug exposure by the total follow-up, CRC diagnosis until end of follow-up. A MPR of 80% or more was regarded as adherent to the specific drug.

Table 1. Baseline characteristics of the study population according to medication use after CRC diagnosis (n=1,043) (Continued).

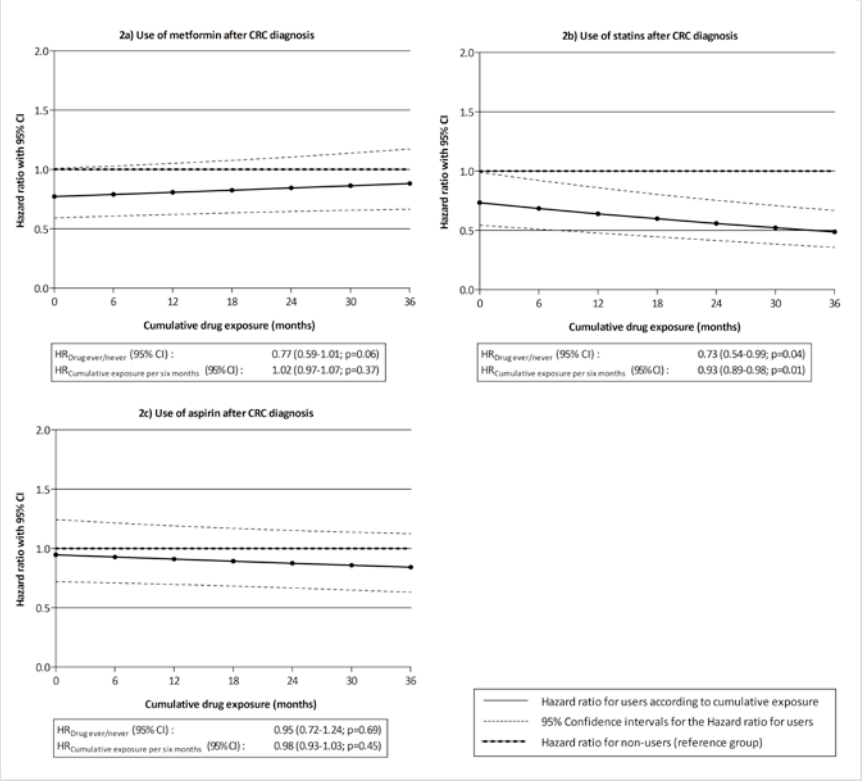
	Total		Metformin users (n=666)		Statin users (n=639)		Aspirin users (n=490)	
	n	(%)	n	(%)	n	(%)	n	(%)
Use of other frequently prescribed drugs in individuals with diabetes after CRC diagnosis [b]								
Sulfonylurea derivatives	606	(58)	439	(66)	384	(60)	301	(61)
Insulin	368	(35)	224	(34)	251	(39)	189	(39)
Other GLDs	82	(8)	65	(10)	61	(10)	49	(10)
Diuretics	491	(47)	321	(48)	325	(51)	256	(52)
Beta blocking agents	465	(45)	334	(50)	337	(53)	276	(56)
Renin-angiotensin system agents	557	(53)	405	(61)	416	(65)	307	(63)
Type of CRC								
Proximal colon	439	(42)	267	(40)	251	(39)	193	(39)
Distal colon	295	(28)	194	(29)	176	(28)	144	(30)
Rectal	309	(30)	205	(31)	212	(33)	153	(31)
TNM stage [c]								
I	204	(20)	133	(20)	138	(22)	99	(20)
II	325	(31)	209	(31)	207	(32)	170	(35)
III	251	(24)	172	(26)	153	(24)	112	(23)
IV	189	(18)	112	(17)	100	(16)	73	(15)
Period of CRC diagnosis								
1998-2002	123	(12)	67	(10)	45	(7)	65	(13)
2003-2007	402	(39)	260	(39)	252	(39)	196	(40)
2008-2011	518	(50)	339	(51)	342	(54)	229	(47)
Treatment of CRC								
Surgery	891	(85)	580	(87)	571	(89)	430	(88)
Chemotherapy	225	(22)	157	(24)	149	(23)	92	(19)
Radiotherapy	196	(19)	134	(20)	140	(22)	99	(20)

[b] Ever use of other drugs after CRC diagnosis (mean follow-up 3.4 ± 3.0 years): sulfonylurea derivatives (ATC-code: A10BB), insulin (ATC-code: A10A), other GLDs, diuretics (ATC-code: C03), beta blocking agents (ATC-code: C07) and drugs for renin-angiotensin system (ATC-code: C09); [c] Does not add up to total due to missings.

Full model

The multivariable time-dependent analysis seemed to suggest that ever-users of metformin had lower overall mortality compared to those never using metformin after CRC diagnosis, though this did not reach statistical significance ($HR_{Drug\ ever/never}$ 0.78; 95% CI 0.59-1.01; p=0.06) (Table 2 and Figure 2). However, in patients using metformin after CRC diagnosis longer cumulative exposure was not associated with overall mortality ($HR_{Cumulative\ exposure\ per\ six\ months}$ 1.02; 95% CI 0.97-1.07; p=0.4). Furthermore, analysis revealed that overall mortality was in

Figure 2. Hazard Ratio's of overall mortality of CRC patients using metformin, statins or aspirin compared to those not using the specific drug after CRC diagnosis according to cumulative drug exposure per six months.*



* Full model, adjusted for use of metformin, sulfonylurea derivatives, insulin, other diabetes medication, statins and aspirin after diagnosis as time-dependent cumulative exposure and as time-dependent ever-never terms, the use of these drugs before diagnosis as a dichotomised variable, and the time-fixed variables: sex, age at CRC diagnosis, calender year of CRC diagnosis, type of CRC, stage at CRC diagnosis and administration of surgery, radiotherapy and/or chemotherapy.

Table 2. Multivariable Cox regression analyses of the time-dependent effect of cumulative exposure to metformin, statins and aspirin per six months of use after CRC diagnosis on overall mortality.

		Metformin				Statins				Aspirin			
		$HR_{Drug\ ever/never}$		$HR_{Cumulative\ exposure\ per\ six\ months}$		$HR_{Drug\ ever/never}$		$HR_{Cumulative\ exposure\ per\ six\ months}$		$HR_{Drug\ ever/never}$		$HR_{Cumulative\ exposure\ per\ six\ months}$	
Model of exposure after CRC diagnosis	n	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Full model [a]	1,043	0.78	(0.59-1.01)	1.02	(0.97-1.07)	0.73	(0.54-0.99) *	0.94	(0.89-0.98) *	0.96	(0.73-1.26)	0.98	(0.94-1.03)
Subgroup analyses[b]													
Colon cancer patients	734	0.72	(0.52-0.99) *	1.01	(0.95-1.07)	0.84	(0.58-1.20)	0.93	(0.88-0.99) *	0.76	(0.55-1.06)	0.98	(0.93-1.05)
Rectal cancer patients	309	0.71	(0.42-1.20)	1.04	(0.94-1.14)	0.61	(0.35-1.08)	0.92	(0.83-1.02)	1.49	(0.86-2.60)	1.00	(0.90-1.10)
Patients who received chemotherapy	225	0.61	(0.33-1.13)	1.05	(0.90-1.22)	1.13	(0.58-2.22)	0.84	(0.70-1.00)	1.36	(0.68-2.71)	0.97	(0.81-1.16)
Sensitivity analyses[b]													
Incident users of all studied drugs[c]	667	0.84	(0.60-1.18)	1.02	(0.95-1.08)	0.67	(0.44-1.00)	0.93	(0.86-1.00)	0.90	(0.62-1.29)	0.96	(0.89-1.03)
Patients > 6 months of follow-up after CRC	859	0.76	(0.54-1.07)	1.01	(0.96-1.06)	0.67	(0.46-0.98) *	0.93	(0.88-0.98) *	1.09	(0.77-1.53)	0.99	(0.93-1.04)
Adjustment for diuretics, beta blocking agents and renin-angiotensin system agents[d]	1,043	0.78	(0.60-1.02)	1.02	(0.97-1.07)	0.71	(0.53-0.97) *	0.93	(0.88-0.98) *	0.94	(0.71-1.23)	0.97	(0.92-1.02)
Adjustment for drug adherence (MPR ≥ 80%)[e]	1,043	0.79	(0.60-1.04)	1.02	(0.97-1.07)	0.75	(0.55-1.02)	0.94	(0.89-0.98) *	0.93	(0.70-1.23)	0.99	(0.94-1.03)
Dealing with stopping statin use prior to death (i.e. sick stopper bias)[f]	1,043	0.78	(0.60-1.02)	1.02	(0.97-1.07)	0.71	(0.53-0.96) *	0.95	(0.90-1.00) *	0.96	(0.73-1.26)	0.98	(0.93-1.03)

[a] Full model, adjusted for use of metformin, sulfonylurea derivatives, insulin, other diabetes medication, statins and aspirin after diagnosis as time-dependent cumulative exposure and as time-dependent ever-never terms, the use of these drugs before diagnosis as a dichotomized variable, and the time-fixed variables: sex, age at CRC diagnosis, calender year of CRC diagnosis, type of CRC, stage at CRC diagnosis and administration of surgery, radiotherapy and/or chemotherapy; [b] Multivariable subgroup or sensitivity analyses with similar variables as in the full model; [c] Prevalent users (those started with metformin, statins or aspirin somewhere before inclusion in the study cohort) were excluded; [d] The time-dependent cumulative exposure, time-dependent ever-never terms after CRC diagnosis and the dichotomized variable for drug use before CRC diagnosis for the use of diuretics, beta blocking agents and renin-angiotensin system agents were added to the full model; [e] Variables for drug adherence (0 = no drug use; 1 = MPR ≥ 80%; 2 = MPR < 80%) for all studied drugs were added to the full model; [f] In this sensitivity analysis the cumulative exposure to statins was adjusted when patients were exposed to statins within the 6 months prior to death. The total period of these 6 months prior to death was included as exposed time to statins. * $p<0.05$.

favour of ever-users of statins compared to those never using statins after cancer diagnosis ($HR_{Drug\ ever/never}$ 0.73; 95% CI 0.54-0.99; p=0.04). Importantly, cumulative exposure to statins was also associated with better overall mortality ($HR_{Cumulative\ exposure\ per\ six\ months}$ 0.94; 95% CI 0.89-0.98; p=0.01). We did not observe differences between ever and never-users of aspirin ($HR_{Drug\ ever/never}$ 0.96; 95% CI 0.73-1.26; p=0.7) nor an effect of cumulative exposure on overall mortality ($HR_{Cumulative\ exposure\ per\ six\ months}$ 0.98; 95% CI 0.94-1.03; p=0.5).
In the full model, the cumulative exposures to other GLDs that were included did not show any association with overall mortality (Appendix 2). Moreover, no significant interactions were found between metformin, statins and aspirin use after CRC diagnosis.

Subgroup- and sensitivity analyses

The effect of metformin on overall mortality in the full model was comparable with the hazard ratios found for ever-never use of metformin and cumulative exposure to metformin in subgroup- and sensitivity analyses (Table 2). The HR of 0.94 for the association between cumulative exposure to statins and overall mortality was approximately similar in all subgroup- and sensitivity analyses and seemed to be even more protective among CRC patients who received chemotherapy ($HR_{Cumulative\ exposure\ per\ six\ months}$ 0.84; 95% CI 0.70-1.00; p=0.05) (Table 2). In sensitivity analyses, excluding prevalent users, patients with less than 6 months of follow up, if adjusted for important cardiovascular co-medication or for drug adherence, the hazard ratios remained borderline significant for the effect of cumulative exposure to statins on overall mortality (Table 2). In the sensitivity analysis in which we adjusted the cumulative exposure to statins when patients stopped with statins in the six months prior to their death, cumulative exposure to statins was still associated with overall mortality, though less clear ($HR_{Cumulative\ exposure\ per\ six\ months}$ 0.95; 95% CI 0.90-1.00; p=0.03) (Table 2). Subgroup- or sensitivity analyses did not reveal different effects of aspirin use on overall mortality than was seen already in the full model (Table 2).

Discussion

This population based study revealed that among CRC patients who started using GLDs before cancer diagnosis, cumulative exposure to metformin or aspirin was not associated with overall mortality, while longer cumulative exposure to statins was independently associated with lower overall mortality, suggesting a drug effect of statins in CRC patients with diabetes. In contrast, we did not observe an independent association between metformin or aspirin use and overall mortality. This might imply that the survival benefit, seen in recently reported studies[1,4-7,11-14], may not be induced by these drugs, but could be the result of suboptimal

methodology or confounded by the prognostic differences between ever and never users of metformin and aspirin. Regarding the use of aspirin and statins, it should be noted that this study only investigated a subgroup, i.e. the diabetic individuals, though a large one, of all statin and aspirin users.

Although many of the earlier observational studies supported the hypothesis that metformin is linked with lower overall mortality in patients with CRC[1-7], today we understand that many of them with impressive hazard rates contained time-related biases and other limitations that artificially made metformin look like a 'wonderdrug' for the survival after cancer[19,21,26,27.] The most important limitation of these studies is that they did not include a time-dependent cumulative exposure variable for drug exposure, which was needed since the effect of exposure depends on duration of use and timing in relationship to the event[28]. Nevertheless, they formed the driving force for the conduct of randomised metformin trials[29,30]. Similar considerations should have been made in studies on aspirin use and mortality after cancer, while some of these studies used pharmacy records, unfortunately, exposure was not analysed as continuous cumulative exposure[11-14]. As a result, it is likely that our analyses showed results more comparable with randomised controlled trials than previous studies in CRC patients[1,4-7,11-14.] Although with the inclusion of time-dependent ever-never terms for the studied drugs in the model, the hazard ratio of the cumulative effect term seems to be not dependent on the events in the unexposed group[31], the inclusion of these terms is still subject of recent debate. Some experts in the field fear that the inclusion of both cumulative exposure and ever-never terms in a model introduces collinearity. Nevertheless, per six months of cumulative metformin use or aspirin use the hazard rate for overall mortality in CRC patients did not change, thus in this study the use of metformin and aspirin was not associated with mortality.

Observational studies have investigated the association between statin use and outcomes among CRC patients regardless of diabetes status, but findings were inconsistent[8-10]. Such discrepancies are likely a result of methodological limitations within observational studies comparable with those in studies on metformin effect. A pooled meta-analysis of 27 randomised trials of statin therapy, did not reveal an effect of statin on cancer risk and mortality[32]. In the current study we investigated a selection of statin users from daily practice, thus comparing our results with previous studies on statin use and mortality after cancer patients might be incorrect. Statins are drugs of prevention and sicker patients with a poorer prognosis might be more likely to discontinue preventative treatments for non-symptomatic illness[25]. Since pharmacy records provide no ascertainment whether patients are compliant with their medication prescriptions, our results might be biased. In our

study after adjusting for the medication possession ratio and after dealing with the discontinuation of statin treatment just before death (by changing unexposed time after discontinuation into exposed time), this study still revealed a protective effect of statins on overall mortality among CRC patients. Unfortunately there is no consensus on the optimal approach to avoid sick stopper bias[25,33,34], thus this remains an important limitation of our study. Although we performed several corrections for time-exposure related confounding risk factors, these findings do not necessarily imply a causal relationship between the use of statins and better overall mortality in CRC patients. Our analyses do not exclude that the association between the use of statins and the reduced risk of mortality in our dataset are partly due to residual confounding.

Several epidemiological studies have been interested in the potential of statins as a chemo preventative, since statins may interact with various signaling pathways that are critical for CRC development as well as progression[35-39]. The favourable effect of statins seemed to increase more clearly with cumulative drug exposure among patients who received chemotherapy, but the effect was only borderline statistically significant. However, our study seems to support the hypothesis that statins (HMG-CoA reductase inhibitors), widely used for the treatment of hypercholesterolemia, might act as a chemo preventative agent[40]. Statins inhibit the conversion of HMG-CoA to the cholesterol precursor mevalonate, which is the rate-limiting step in cholesterol biosynthesis[35]. Mevalonate is the precursor compound for other isoprenoids, which are critical for the modification of proteins involved in cell growth, including both the RAS and RHO oncogenes[35]. These potential antineoplastic benefits of statins were studied with regard to chemotherapy and radiotherapy administration, though this was only studied irrespective of diabetes status[36-39]. Two studies in rectal cancer patients revealed that the use of statins was associated with improved pathologic response after neoadjuvant chemoradiation[36,37]. These findings were supported by cell line studies, since lovastatin augmented apoptosis induced by chemotherapeutic agents such as 5-FU and cisplatin in colon cancer cells[38,39].

Unfortunately, the number of patients included for sub-analyses was rather small and the follow-up was short, therefore additional evidence in a greater subset of patients with longer follow-up is needed. In addition, since no information was available on cause of mortality, we were not able to verify whether use of metformin, statins and aspirin is associated with a decreased cancer specific mortality. The protective effect of statin use on overall mortality in this study might be highly attributed to the decrease in cardiovascular deaths instead of cancer deaths in this group of patients[40]. Since the data from clinical laboratories were only available

for a subpopulation of the cohort, we were not able to include information on cholesterol levels, values and body mass index in the analyses which is a major limitation. The influence of these metabolic factors on overall mortality in GLD users might be of interest and should be evaluated in future studies.

In conclusion, longer cumulative exposure to metformin or aspirin was not associated with overall mortality among CRC patients. But, longer cumulative exposure to statins after the diagnosis of CRC was associated with lower overall mortality among CRC patients starting on GLDs before cancer diagnosis. Our findings support a protective effect of statins, independent of metformin and aspirin use, in CRC patients using GLDs. As this study had an observational design our results are based on the decision of a clinician to prescribe a certain type of drugs, based on the patient characteristics together with the experience of the clinician. The findings of the current study requires to elucidate this association in future randomized, and in-depth studies, with larger study populations dealing with the mentioned pharmaco-epidemiological challenges, sick stopper bias and adjusting for additional metabolic characteristics.

References

1. Garrett CR, Hassabo HM, Bhadkamkar NA, Wen S, Baladandayuthapani V, Kee BK, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012;106(8):1374-8.
2. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care. 2010;33(2):322-6.
3. Bo S, Ciccone G, Rosato R, Villois P, Appendino G, Ghigo E, et al. Cancer mortality reduction and metformin: a retrospective cohort study in type 2 diabetic patients. Diabetes Obes Metab. 2012;14(1):23-9.
4. Lee JH, Kim TI, Jeon SM, Hong SP, Cheon JH, Kim WH. The effects of metformin on the survival of colorectal cancer patients with diabetes mellitus. Int J Cancer. 2011;131(3):752-9.
5. Spillane S, Bennett K, Sharp L, Barron TI. A cohort study of metformin exposure and survival in patients with stage I-III colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2013;22(8):1364-73.
6. Cossor FI, Adams-Campbell LL, Chlebowski RT, Gunter MJ, Johnson K, Martell RE, et al. Diabetes, metformin use, and colorectal cancer survival in postmenopausal women. Cancer Epidemiol. 2013;37(5):742-9.
7. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299-304.
8. Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. Gut. 2010;59(11):1572-85.
9. Siddiqui AA, Nazario H, Mahgoub A, Patel M, Cipher D, Spechler SJ. For patients with colorectal cancer, the long-term use of statins is associated with better clinical outcomes. Dig Dis Sci. 2009;54(6):1307-11.
10. Lakha F, Theodoratou E, Farrington SM, Tenesa A, Cetnarskyj R, Din FV, et al. Statin use and association with colorectal cancer survival and risk: case control study with prescription data linkage. BMC Cancer. 2012;12:487.
11. Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJ, van Herk-Sukel MP, Lemmens V, et al. Use of aspirin postdiagnosis improves survival for colon cancer patients. Br J Cancer. 2012;106(9):1564-70.
12. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 2009;302(6):649-58.
13. Walker AJ, Grainge MJ, Card TR. Aspirin and other non-steroidal anti-inflammatory drug use and colorectal cancer survival: a cohort study. Br J Cancer. 2012;107(9):1602-7.
14. McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. Eur J Cancer. 2013;49(5):1049-57.
15. van Dijk L, Wolters I, de Bakker DH. NIVEL: Farmaceutische zorg in de integrale bekostiging, http://www.nivel.nl/sites/default/files/bestanden/Rapport-Farmaceutische-zorg-in-tegrale-bekostiging.pdf. 2011.
16. Ekstrom N, Cederholm J, Zethelius B, Eliasson B, Fharm E, Rolandsson O, et al. Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register. BMJ Open. 2013;3(4).
17. Smiechowski B, Azoulay L, Yin H, Pollak MN, Suissa S. The use of metformin and colorectal cancer incidence in patients with type II diabetes mellitus. Cancer Epidemiol Biomarkers Prev. 2013;22(10):1877-83.
18. Yu O, Eberg M, Benayoun S, Aprikian A, Batist G, Suissa S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol. 2014;32(1):5-11.
19. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care. 2012;35(12):2665-73.
20. Zanders MM, Vissers PA, van de Poll-Franse LV. Association between metformin use and mortality in patients with prostate cancer: explained by confounding by indication? J Clin Oncol. 2014;32(7):701.
21. Walker JJ, Johnson JA, Wild SH. Diabetes treatments and cancer risk: the importance of considering aspects of drug exposure. Lancet Diabetes Endocrinol. 2013;1(2):132-9.
22. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395-404.

23. World Health Organization. Collaborating Centre for Drug Statistics Methodology - ATC/DDD index. Accessed at www.whocc.no/atc_ddd_index, 2014.
24. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. Med Care. 2008;46(11):1125-33.
25. Stavrou EP, Buckley N, Olivier J, Pearson SA. Discontinuation of statin therapy in older people: does a cancer diagnosis make a difference? An observational cohort study using data linkage. BMJ Open. 2012;2(3).
26. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-32.
27. Suissa S, Azoulay L. Metformin and cancer: mounting evidence against an association. Diabetes Care. 2014;37(7):1786-8.
28. Stricker BH, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. Eur J Epidemiol. 2010;25(4):245-51.
29. http://www.clinicaltrials.gov, A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer, NCT01101438.
30. http://www.clinicaltrials.gov, A Trial of Standard Chemotherapy With Metformin (vs Placebo) in Women With Metastatic Breast Cancer, NCT01310231.
31. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012;55(11):2929-37.
32. Cholesterol Treatment Trialists Collaboration, Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS One. 2012;7(1):e29849.
33. Wang SV, Gagne JJ, Glynn RJ, Schneeweiss S. Case-crossover studies of therapeutics: design approaches to addressing time-varying prognosis in elderly populations. Epidemiology. 2013;24(3):375-8.
34. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology. 2001;12(6):682-9.
35. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature. 1990;343(6257):425-30.
36. Mace AG, Gantt GA, Skacel M, Pai R, Hammel JP, Kalady MF. Statin therapy is associated with improved pathologic response to neoadjuvant chemoradiation in rectal cancer. Dis Colon Rectum. 2013;56(11):1217-27.
37. Katz MS, Minsky BD, Saltz LB, Riedel E, Chessin DB, Guillem JG. Association of statin use with a pathologic complete response to neoadjuvant chemoradiation for rectal cancer. Int J Radiat Oncol Biol Phys. 2005;62(5):1363-70.
38. Agarwal B, Bhendwal S, Halmos B, Moss SF, Ramey WG, Holt PR. Lovastatin augments apoptosis induced by chemotherapeutic agents in colon cancer cells. Clin Cancer Res. 1999;5(8):2223-9.
39. Kodach LL, Jacobs RJ, Voorneveld PW, Wildenberg ME, Verspaget HW, van Wezel T, et al. Statins augment the chemosensitivity of colorectal cancer cells inducing epigenetic reprogramming and reducing colorectal cancer cell 'stemness' via the bone morphogenetic protein pathway. Gut. 2011;60(11):1544-53.
40. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339(19):1349-57.

Appendix 1. Baseline characteristics of the study population according to medication use after CRC diagnosis (n=1,043).

	Metformin use (n=666; 64%)		No metformin use (n=377; 36%)		Statin use (n=639; 61%)	
	n	(%)	n	(%)	n	(%)
Age at CRC diagnosis (years; means (SD))	72.3	(± 8.8)	74.8	(± 9.5) **	71.9	(± 8.5)
Male	366	(55)	177	(47) *	377	(59)
Duration of GLD use at CRC diagnosis						
< 1 years	74	(11)	34	(9)	63	(10)
1 – 3 years	110	(16)	58	(15)	103	(16)
≥ 3 years	225	(34)	106	(28)	206	(32)
Prevalent user	257	(39)	179	(48) *	267	(42)
Duration of follow-up (years; means (SD))	3.7	(± 3.0)	2.9	(± 2.9) **	3.8	(± 3.0)
End of follow-up (%)						
Death	272	(41)	222	(59)	223	(35)
Loss to follow-up	7	(1)	4	(1)	7	(1)
End of study (31-12-2011)	387	(58)	151	(40) **	409	(64)
Use of the drugs under study after CRC diagnosis						
Metformin	666	(100)	0	(0)	469	(73)
Duration of metformin use (years; median (IQR))	1.6	(0.5-3.3)			1.9	(0.7-3.6)
Adherent users (MPR ≥ 80%) [a]	364	(55)			260	(55)
Statins	469	(70)	170	(45)	469	(100)
Duration of statin use (years; median (IQR))	2.2	(0.8-4.1)	1.2	(0.2-3.4)*	2.0	(0.5-3.9)
Adherent users (MPR ≥ 80%) [a]	273	(58)	83	(49) *	356	(56)
Aspirin	336	(51)	154	(41) *	359	(56)
Duration of aspirin use (years; median (IQR))	1.6	(0.2-3.5)	1.0	(0.2-2.8)*	1.7	(0.2-3.6)
Adherent users (MPR ≥ 80%) [a]	167	(50)	68	(44)	174	(48)
Use of the drugs under study before CRC diagnosis						
Metformin	591	(89)	145	(38) **	480	(75)
Prevalent user (% of metformin use)	128	(22)	30	(21)	103	(21)
Statins	437	(66)	200	(53) **	556	(87)
Prevalent user (% of statin use)	111	(25)	71	(35) *	164	(29)
Aspirin	305	(46)	162	(43)	326	(51)
Prevalent user (% of aspirin use)	108	(35)	81	(49) *	131	(39)

[a] MPR: Medication Possession Ratio, calculated for each patient by dividing the cumulative days of drug exposure by the total follow-up, CRC diagnosis until end of follow-up. A MPR of 80% or more was regarded as adherent to the specific drug; * p<0.05; ** p<0.0001.

	No statin use (n=404; 39%)		Aspirin use (n=490; 47%)		No aspirin use (n=553; 53%)		All drugs used (n=257; 25%)		None of drugs used (n=155; 15%)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	75.3	(± 9.6) **	73.5	(± 8.8)	72.9	(± 9.4)	72	(± 8.2)	75.1	(±10.2) *
	166	(41) **	284	(58)	259	(47) *	167	(65)	58	(37) **
	45	(11)	50	(10)	58	(11)	32	(12)	19	(12)
	65	(16)	68	(14)	100	(18)	36	(14)	25	(16)
	125	(31)	153	(31)	178	(32)	84	(33)	47	(30)
	169	(42)	219	(45)	217	(39)	105	(41)	64	(41)
	2.7	(± 2.9) **	3.9	(± 3.2)	2.9	(± 2.7) **	4.1	(± 3.0)	2.0	(± 2.3) **
	271	(67)	219	(45)	275	(50)	80	(31)	103	(67)
	4	(1)	3	(1)	8	(1)	2	(1)	2	(1)
	129	(32) **	268	(54)	270	(49)	175	(68)	50	(32) **
	197	(49) **	336	(69)	330	(60) *	666	(100)	0	(0)
	1.1	(0.2-2.4)**	1.9	(0.6-3.6)	1.4	(0.4-3.0)*	2.1	(0.7-3.7)		
	104	(53)	178	(53)	186	(56)	139	(54)		
	0	(0)	359	(73)	280	(51) **	469	(100)	0	(0)
			2.2	(0.7-4.2)	1.8	(0.5-3.6)*	2.4	(1.0-4.4)		
			204	(57)	152	(54)	153	(60)		
	131	(32) **	490	(100)	0	(0)	490	(100)	0	(0)
	0.9	(0.1-2.3) *	1.5	(0.2-3.4)			1.9	(0.3-3.6)		
	61	(47)	235	(48)			130	(51)		
	256	(63) **	336	(69)	400	(72)	227	(88)	73	(47) **
	55	(21)	80	(24)	78	(20)	53	(23)	11	(15)
	81	(20) **	342	(70)	295	(53) **	222	(86)	40	(26) **
	18	(22)	111	(32)	71	(24) *	68	(30)	10	(24)
	141	(35) **	386	(79)	81	(15) **	199	(77)	27	(17) **
	58	(40)	156	(40)	33	(37)	72	(36)	10	(33)

Appendix 1. Baseline characteristics of the study population according to medication use after CRC diagnosis (n=1,043) (Continued).

	Metformin use (n=666; 64%)		No metformin use (n=377; 36%)		Statin use (n=639; 61%)	
	n	(%)	n	(%)	n	(%)
Use of other frequently prescribed drugs in individuals with diabetes after CRC diagnosis [b]						
Sulfonylurea derivatives	439	(66)	167	(44) **	384	(60)
Insulin	224	(34)	144	(38)	251	(39)
Other GLDs	65	(10)	17	(5) *	61	(10)
Diuretics	321	(48)	170	(45)	325	(51)
Beta blocking agents	334	(50)	131	(35) **	337	(53)
Renin-angiotensin system agents	405	(61)	152	(40) **	416	(65)
Type of CRC						
Proximal colon	267	(40)	172	(46)	251	(39)
Distal colon	194	(29)	101	(27)	176	(28)
Rectal	205	(31)	104	(27)	212	(33)
TNM stage [c]						
I	133	(20)	71	(19)	138	(22)
II	209	(31)	116	(31)	207	(32)
III	172	(26)	79	(21)	153	(24)
IV	112	(17)	77	(20)	100	(16)
Period of CRC diagnosis						
1998-2002	67	(10)	56	(15)	45	(7)
2003-2007	260	(39)	142	(38)	252	(39)
2008-2011	339	(51)	179	(47)	342	(54)
Treatment of CRC						
Surgery	580	(87)	311	(82) *	571	(89)
Chemotherapy	157	(24)	68	(18) *	149	(23)
Radiotherapy	134	(20)	62	(16)	140	(22)

[b] Ever use of other drugs after CRC diagnosis (mean follow-up 3.4 ± 3.0 years): sulfonylurea derivatives (ATC-code: A10BB), insulin (ATC-code: A10A), other GLDs, diuretics (ATC-code: C03), beta blocking agents (ATC-code: C07) and drugs for renin-angiotensin system (ATC-code: C09); [c] Does not add up to total due to missings; * $p<0.05$; ** $p<0.0001$.

	No statin use (n=404; 39%)		Aspirin use (n=490; 47%)		No aspirin use (n=553; 53%)		All drugs used (n=257; 25%)		None of drugs used (n=155; 15%)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
	222	(55)	301	(61)	305	(55) *	170	(66)	58	(37) **
	117	(29) *	189	(39)	179	(32) *	97	(37)	40	(26) *
	21	(5) *	49	(10)	33	(6) *	29	(11)	4	(3) *
	166	(41) *	256	(52)	235	(43) *	129	(50)	45	(29) **
	128	(32) **	276	(56)	189	(34) **	155	(60)	25	(16) **
	141	(35) **	307	(63)	250	(45) **	182	(71)	31	(20) **
	188	(47)	193	(39)	246	(45)	94	(37)	77	(50)
	119	(29)	144	(30)	151	(27)	72	(28)	38	(24)
	97	(24) *	153	(31)	156	(28)	91	(35)	40	(26) *
	66	(16)	99	(20)	105	(19)	58	(23)	22	(14)
	118	(29)	170	(35)	155	(28)	88	(34)	42	(27)
	98	(24)	112	(23)	139	(25)	60	(23)	38	(25)
	89	(22) **	73	(15)	116	(21)	34	(13)	37	(24) *
	78	(19)	65	(13)	58	(11)	18	(7)	26	(17)
	150	(37)	196	(40)	206	(37)	107	(42)	50	(32)
	176	(44) **	229	(47)	289	(52)	132	(51)	79	(51) *
	320	(79) **	430	(88)	461	(83) *	230	(89)	120	(77) *
	76	(19)	92	(19)	133	(24) *	56	(22)	33	(21)
	56	(14) *	99	(20)	97	(18)	60	(23)	21	(14) *

Appendix 2. Multivariable Cox regression analyses with the hazard ratios for the full model.

Variables within full model	HR	(95% CI)
Ever use after cancer diagnosis (ever versus never)		
Metformin	0.78	(0.59-1.01)
Statins	0.73	(0.54-0.99) *
Aspirin	0.96	(0.73-1.26)
Sulfonylurea derivatives	0.83	(0.63-1.10)
Insulin	2.09	(1.52-2.88) **
Other GLDs	0.69	(0.38-1.26)
Cumulative exposure per six months of use after cancer diagnosis		
Metformin	1.02	(0.97-1.07)
Statins	0.94	(0.89-0.98) *
Aspirin	0.98	(0.94-1.03)
Sulfonylurea derivatives	1.02	(0.97-1.07)
Insulin	1.00	(0.95-1.06)
Other GLDs	1.10	(0.93-1.31)
Ever use before cancer diagnosis (ever versus never)		
Metformin	1.10	(0.85-1.45)
Statins	0.95	(0.71-1.27)
Aspirin	1.33	(1.03-1.67) *
Sulfonylurea derivatives	1.27	(0.97-1.67)
Insulin	0.47	(0.33-0.67) **
Other GLDs	0.72	(0.50-1.03)
Age (years)	1.04	(1.03-1.05) **
Male (female is reference)	1.40	(1.16-1.70) *
Year of cancer diagnosis (years)	0.96	(0.93-0.99) *
Cancer treatment		
Received surgery (no is reference)	0.24	(0.18-0.32) **
Administration of chemotherapy (no is reference)	0.59	(0.46-0.77) **
Administration of radiotherapy (no is reference)	0.61	(0.44-0.83) *
Cancer stage		
I	Ref	
II	0.86	(0.65-1.13)
III	2.37	(1.79-3.14) **
IV	4.49	(3.31-6.10) **
Cancer type		
Proximal colon tumour	Ref	
Distal colon tumour	0.97	(0.77-1.21)
Rectal tumour	1.11	(0.84-1.46)

* $p<0.05$; ** $p<0.0001$.

8

Impact of cancer diagnosis and treatment on glycaemic control among individuals with colorectal cancer using glucose lowering drugs

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Abstract

Aims: In our search to understand why patients with diabetes and cancer have deteriorated survival rates, this study aims to evaluate the impact of cancer diagnosis and its treatment on HbA_{1c}-values among individuals with colorectal cancer (CRC) using glucose lowering drugs (GLDs).

Materials and methods: Patients with primary CRC (1998-2011) were selected from the Eindhoven Cancer Registry and linked to drug dispensing data from the PHARMO Database Network. GLDs users for more than two years prior to cancer diagnosis were selected. Linear mixed effects models were conducted to evaluate changes in HbA_{1c} for colon cancer (CC) and rectal cancer (RC) patients separately in the four years around CRC diagnosis.

Results: From all CRC patients (n=4,714), 294 (6%) users of GLDs with CC and 144 (3%) with RC were selected. In the crude model, the mean HbA_{1c} at cancer diagnosis was 6.9% (51.6 mmol/mol) among CC patients and 7.1% (53.5 mmol/mol) among RC patients. In the adjusted model HbA_{1c} decreased with 0.12% per year (1.3 mmol/mol; p=0.0002) before cancer diagnosis for CC patients and after cancer diagnosis it increased with 0.12% per year (1.3 mmol/mol; p=0.02). Before the diagnosis of RC HbA_{1c} decreased with 0.18% per year (2.0 mmol/mol; p=0.0006), whereas after cancer diagnosis it changed not-significantly with +0.04% per year (0.4 mmol/mol; p=0.59). Effects on HbA_{1c} were more pronounced in those with proximal colon tumours and users of anti-anaemic preparations before CC diagnosis.

Conclusions: Among CRC patients who used GLDs, HbA_{1c} levels before cancer diagnosis decreased with 0.12%-0.18% (1-2 mmol/mol) per year and after cancer diagnosis they increased only among CC patients (0.12% per year; 1.3 mmol/mol). Physicians should be aware that HbA_{1c} levels among diabetics might decrease because of cancer diagnosis. However, the HbA_{1c} measure might be inappropriate for visualising glycaemic control in (un)diagnosed cancer patients that frequently use anti-anaemic preparations.

Introduction

Accumulating evidence suggests that colorectal cancer (CRC) is more common in individuals with diabetes than in those without[1-4] and also, that individuals with diabetes have worse overall survival after CRC compared to those without diabetes, with five-year survival rates of 35% and 48%, respectively[5-13]. Although numerous hypotheses for this worse survival were studied, all of them focussed on the effect of diabetes and its treatment on cancer, while the development of a tumour and the treatment of cancer may also influence diabetes control. The presence of cancer might result in worse glycaemic control, changes in glucose lowering drugs (GLDs), patient adherence and diabetes complications, indirectly resulting in worse survival. However, to our knowledge, till now these hypotheses are only speculations and not investigated properly. The glycaemic control in individuals with diabetes is checked every three to six months, depending on the degree of glycaemic control, by using the HbA_{1c} measurement[14]. HbA_{1c} is the most widely used clinical test and represents the average amount of change in glycated haemoglobin, thereby indicating the mean blood glucose concentration over the life span of a red blood cell, which is approximately three months[15]. Changes in this lifespan can affect HbA_{1c}, rapid red cell turnover leads to a greater proportion of younger red cells and falsely low HbA_{1c} levels. Consequently, the treatments for anaemia and iron deficiency might influence the levels of HbA_{1c}[16] and need to be considered since they are frequently prescribed in patients with CRC[17].
The HbA_{1c}-value, as a marker of glycaemic control, might be influenced by cancer, leading to (required or inappropriate) changes in medication. Moreover, the HbA_{1c} measure might be associated with mortality, since studies showed that individuals with diabetes and HbA_{1c} values <6.5% (48 mmol/mol) or with HbA_{1c} values >9.0% (75 mmol/mol) had higher mortality in the year after these values compared to those with recent 'normal' HbA_{1c} values between 6.5% and 9%[18,19]. The higher mortality among individuals with low HbA_{1c} values might be the result of morbidity and the frequent occurrence of hypoglycaemia, whereas among those with high HbA_{1c} values the increased risk of diabetes complications might cause the higher mortality[20,21]. If the presence of cancer results in steep decreases and/or increases of HbA_{1c}, this will strengthen the hypothesis that the overall worse survival seen in patients with diabetes and cancer might also be explained by changes in glycaemic control due to cancer.

For the current research, the aim was to assess whether, and to which extent, HbA_{1c} -values change during the process of cancer detection and initial treatment, evaluated in a period of 4 years around the diagnosis of colon cancer (CC) and rectal cancer (RC). Since the treatment for CC and RC differs, i.e. mainly chemotherapy for CC and radiotherapy for RC, these tumours might impact HbA_{1c}

differently. We hypothesised that cancer development and treatment will increase the value of HbA_{1c}, i.e. glycaemic control, during this 4-year period.

Methods

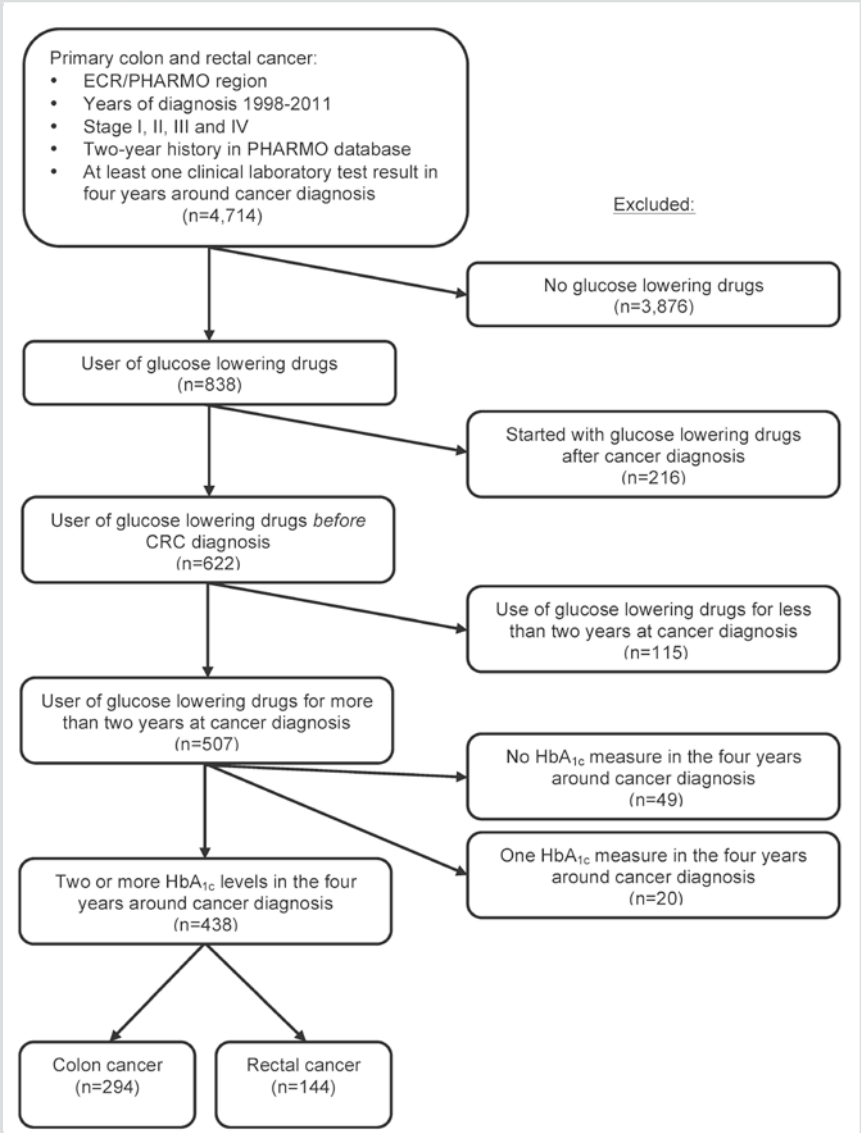
Data sources

Data were obtained from the Eindhoven Cancer Registry (ECR) linked on a patient level to the PHARMO Database Network, covering a demographic region in the Southern part of the Netherlands of approximately one million inhabitants. The construct and validity of the ECR-PHARMO cohort have been described elsewhere[22]. The ECR, maintained by the Netherlands Comprehensive Cancer Organisation (IKNL), records data on all patients newly diagnosed with cancer in the Southern part of the Netherlands, an area with 2.4 million inhabitants. The registry is notified by six pathology departments, 10 community hospitals, and two radiotherapy departments. Trained registration clerks actively collect data on patient characteristics, cancer diagnosis, staging, and initial treatment from hospital medical records. The PHARMO Database Network is a large, patient-centric data network including multiple linked observational databases designed for safety and outcomes research of drugs. For this study the community (out-patient) pharmacy database was used, which includes data on the dispensed drug, dispensing date, amount and regiment dispensed, and thus the duration of use. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification[23]. In addition, the longitudinal data obtained from the clinical laboratories was used, which was available for a sub-cohort of the patients included in the PHARMO Database Network. Both the ECR and the PHARMO Database Network are recognised as high quality sources for epidemiological research that collect information in overlapping regions in the Netherlands for a period of at least 10 years[22].

Study population

The source population included all CC and RC patients registered in the ECR-PHARMO cohort between January 1, 1998 and December 31, 2011. To be eligible these patients needed to have a two-year history in the PHARMO database before their cancer diagnosis and at least one clinical laboratory test result in the four years around their cancer diagnosis (n=4,714) (Figure 1). From this population patients who used any type of glucose lowering drug (GLD; ATC code: A10) for more than two years prior to cancer diagnosis were selected (n=507). These 507 patients were linked to the database of the clinical laboratories with information on HbA_{1c}: only individuals with two or more HbA_{1c} measures in the 4 years around cancer diagnosis were selected for the analyses (n=438). While for all users of GLDs the duration of use was at least two years, only for incident users (n=249;

Figure 1. Flowchart of patients selected for analysis.



57%) the exact duration after these two years was known. For this study, CC (n=294) and RC (n=144) patients were analysed separately.

Co-variables

Patient, tumour and treatment related variables included for adjustment were selected a priori or had shown an independent association ($p<0.05$) with HbA_{1c}. Age at CRC diagnosis, sex, period of CRC diagnosis (year of diagnosis), stage of cancer, receiving surgery, administration of radiotherapy (only for RC) and/or chemotherapy and duration of GLD use at cancer diagnosis (2-4 years; 4-6 years; ≥ 6 years; prevalent use) were considered potential confounders. All covariates were included in the multivariable analyses as time-fixed variables.

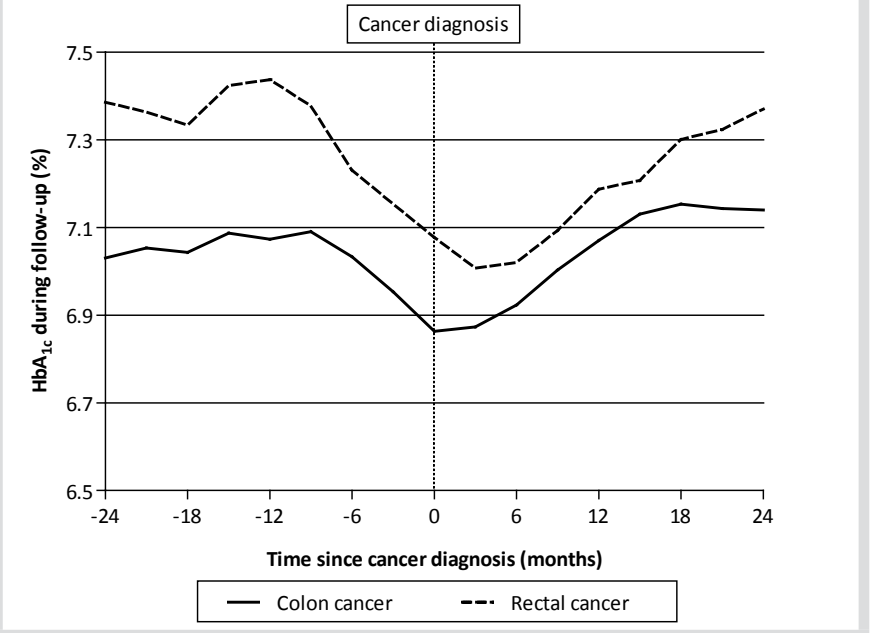
Statistical analysis

Using crude data, we illustrated mean changes in HbA_{1c} during the four years around cancer diagnosis as three-months moving averages in Figure 2.
Linear mixed effects models were analysed to evaluate the course in HbA_{1c} for cancer patients. The multilevel model used had random intercepts and slopes and an unstructured covariance matrix. Time was analysed as a continuous variable, and for the analyses divided into time before and time after cancer diagnosis within one statistical model, because these had different directions of effects on the HbA_{1c} measures. The baseline or intercept of the analyses was set on the diagnosis of CC and RC, respectively, as a result the time (per year) before and after cancer was set off with respect to this baseline. A p-value <0.05 was considered statistically significant.

Subgroup- and sensitivity analyses

To determine the effect of duration of use of GLDs on the association between HbA_{1c} and CRC, users with unknown duration were excluded in these sub-analysis. The presence of effect modification between cancer treatment and HbA_{1c} was evaluated by including interaction terms in our full model (variable of interest * linear time pre diagnosis or * linear time post diagnosis). For interaction terms a p-value <0.1 was considered statistically significant. Since anti-anaemic preparations (ATC-code: B03) might influence HbA_{1c} and are frequently used by CC patients, the use of these preparations before the cancer diagnosis was assessed for effect modification.
Moreover, the type of GLD use was assessed as confounder and potential effect modifier in the association between HbA_{1c} and CRC and divided into those using metformin (ATC-code: A10BA02), sulfonylurea derivatives (ATC-code: A10BB), insulin (ATC-code: A10A) and other GLDs before and after cancer diagnosis separately (i.e. yes-no terms). In two other sensitivity analyses the effect of mean

Figure 2. Values of HbA_{1c} during follow-up as three-months moving averages.



body mass index (BMI) and haemoglobin (Hb) at the time of cancer on the association between HbA_{1c} and CRC was determined by including BMI and Hb as continuous variables in the full model. They were defined as the mean BMI (Kg/m^2) and Hb (mmol/mol) of the measures within the 6 months around CRC diagnosis. In another analyses, the impact of cancer stage (I-III vs. IV) on the association between HbA_{1c} and cancer was explored. All statistical analyses were performed using SAS software (version 9.3, SAS institute, Cary, US).

Results

Within the ECR-PHARMO cohort, out of 4,714 CRC patients diagnosed between 1998 and 2011, 838 patients (18%) were registered using GLDs (Figure 1). Of these, 294 (35%) CC and 144 (17%) RC patients used GLDs more than two years before the diagnosis of cancer. For the proposed analyses mean age at cancer diagnosis was 74.5 ± 8.6 years for CC patients and 72.6 ± 9.1 years for RC patients (Table 1).

The number of HbA_{1c} measurements registered, during the follow-up of four years, was 9.2 ± 5.5 and 9.4 ± 4.5, for CC and RC patients, respectively (Table 1). Moreover, mean Hb at CRC diagnosis was slightly lower for CC compared to RC

Table 1. Characteristics of study population (n=438).

	Colon (n=294)		Rectal (n=144)	
	n	(%)	n	(%)
Patient characteristics				
Age at first GLD dispensing (years; Mean (± SD)) [a]	67.9	(± 8.8)	66	(± 9.4)
Age at cancer diagnosis (years; Mean (± SD))	74.5	(± 8.6)	72.6	(± 9.1)
Duration of GLD use at cancer diagnosis [b]				
Incident use: 2 – 4 years	53	(18)	23	(16)
Incident use: 4 – 6 years	58	(20)	23	(16)
Incident use: ≥ 6 years	65	(22)	27	(19)
Unknown duration, albeit ≥ 2 years	118	(40)	71	(49)
Male	156	(53)	95	(66)
Glucose lowering drug use (yes/no)				
Two years before cancer diagnosis till cancer diagnosis				
Metformin	192	(65)	102	(71)
Sulfonylurea derivatives	177	(60)	86	(60)
Insulin	73	(25)	49	(34)
Other glucose lowering drugs	39	(13)	17	(12)
From cancer diagnosis till two years after cancer diagnosis				
Metformin	157	(53)	90	(63)
Sulfonylurea derivatives	148	(50)	75	(52)
Insulin	89	(30)	60	(42)
Other glucose lowering drugs	26	(9)	10	(7)
Laboratory measures				
Number of HbA_{1c} measurements (Mean (± SD))				
Total number during follow-up	9.2	(± 5.5)	9.4	(± 4.5)
Before cancer diagnosis	5.5	(± 3.0)	5.4	(± 2.5)
After cancer diagnosis	4.8	(± 3.1)	5	(± 2.7)
Mean first HbA_{1c} (%) during follow-up				
< 6.5	95	(32)	38	(27)
≥ 6.5 and < 7.0	57	(19)	22	(15)
≥ 7.0 and < 7.5	58	(20)	35	(24)
≥ 7.5	84	(29)	49	(34)
Mean BMI at cancer diagnosis (n=167; Kg/m^2; Mean (± SD)) [c]	28.1	(± 4.4)	28.6	(± 5.3)
Mean Hb at cancer diagnosis (n=80; mmol/L; Mean (± SD)) [c]	7.0	(± 1.1)	7.7	(± 1.2)
Use of anti-anaemic preparations	87	(30)	17	(12)

GLD: glucose lowering drug; SD: standard deviation; BMI: body mass index; Hb: haemoglobin. [a] Age at first GLD dispensing was defined as age of first GLD dispensing in this cohort, i.e. for prevalent users the age of first GLD dispensing ever is different; [b] Incident users were defined as those that started with GLD after entrance in the ECR-PHARMO cohort, thus with known diabetes duration. Prevalent users were defined as those that started with GLD at any time before entrance in the ECR-PHARMO cohort, thus with unknown diabetes duration; [c] BMI and Hb at diagnosis were defined as BMI and Hb measures within the 6 months around CRC diagnosis and included in the model as continuous variables.

Table 1. Characteristics of study population (n=438) (Continued).

	Colon (n=294)		Rectal (n=144)	
	n	(%)	n	(%)
Tumour characteristics				
Type of colon cancer				
Proximal	166	(56)	n.a.	
Distal	128	(44)	n.a.	
TNM stage				
I	55	(19)	46	(32)
II	108	(37)	28	(19)
III	78	(26)	47	(33)
IV	53	(18)	23	(16)
Period of diagnosis				
2000-2007	100	(34)	53	(37)
2008-2009	102	(35)	52	(36)
2010-2011	92	(31)	92	(27)
Treatment of cancer				
Surgery	267	(91)	125	(87)
Chemotherapy	74	(25)	32	(22)
Radiotherapy	3	(1)	100	(69)

patients (7.0 ± 1.1 vs. 7.7 ± 1.2). Before cancer diagnosis, 87 (30%) CC and 17 (12%) RC patients were dispensed anti-anaemic preparations. Compared to RC patients, those with CC more often had stage II disease and less frequently stage I disease. During a median follow-up of 2.0 years, 81 (28%) patients with CC died and 37 (26%) with RC (data not shown).

Colon cancer

In the crude linear model the intercept, i.e. HbA_{1c} at cancer diagnosis, was 6.9% (51.6 mmol/mol) (Table 2). The full model showed that in the period before cancer diagnosis, the mean HbA_{1c} decreased with 0.12% per year (95% CI 0.06-0.18; 1.3 mmol/mol; p=0.0002), whereas after cancer diagnosis the mean HbA_{1c} increased with 0.12% per year (95% CI 0.02-0.21; 1.3 mmol/mol; p=0.02), which is also illustrated in Figure 2 with the crude data. Among subgroup analyses in CC patients, the effects on HbA_{1c} were more clear for incident GLD users; before the cancer diagnosis a decrease in mean HbA_{1c} of 0.16% per year (95% CI 0.08-0.24; 1.7 mmol/mol; p<0.0001) and after the cancer diagnosis an increase of 0.20% per year (95% CI 0.05 to 0.34; 2.1 mmol/mol; p=0.008) was seen. Subgroup analyses among insulin users showed a higher baseline HbA_{1c} at cancer diagnosis (7.5%; 57.9 mmol/mol), while before and after cancer diagnosis no significant effects on HbA_{1c} were seen (Table 2). The HbA_{1c} values before the diagnosis of cancer seemed to be strongly associated with the presence of a proximal tumour and the use of anti-anaemic preparations (Table 2). In patients using these preparations before cancer diagnosis, the mean HbA_{1c} decreased with 0.25% per year (95% CI

Table 2. HbA_{1c}-values (%) at baseline and changes within the four years around cancer diagnosis (n=438).

		Crude linear model [a]		Adjusted linear model [b]			
		Baseline		Time pre diagnosis (years)		Time post diagnosis (years)	
	Patients	Estimate	(95% CI)	Estimate	(95% CI) [c]	Estimate	(95% CI) [c]
Colon cancer							
All patients	294	6.9	(6.8 to 7.0)	-0.12	(-0.18 to -0.06) *	0.12	(0.02 to 0.21) *
Subgroup analyses							
Incident GLD users	176	6.7	(6.5 to 6.8)	-0.16	(-0.24 to -0.08) **	0.20	(0.05 to 0.34) *
Proximal colon cancer	166	6.9	(6.8 to 7.0)	-0.17	(-0.26 to -0.08) *	0.11	(-0.01 to 0.23)
Distal colon cancer	128	6.8	(6.7 to 7.0)	-0.05	(-0.14 to 0.04)	0.14	(-0.02 to 0.29)
Insulin use prior to CRC	73	7.5	(7.3 to 7.7)	-0.08	(-0.21 to 0.05)	-0.02	(-0.20 to 0.16)
No insulin use prior to CRC	221	6.7	(6.6 to 6.8)	-0.13	(-0.20 to -0.07) *	0.17	(0.06 to 0.29) *
Anti-anaemic drug use prior to CRC	87	6.8	(6.6 to 7.0)	-0.25	(-0.40 to -0.10) *	0.13	(-0.06 to 0.33)
No anti-anaemic drug use prior to CRC	207	6.9	(6.8 to 7.1)	-0.07	(-0.13 to 0.00) *	0.11	(0.00 to 0.21) *
Sensitivity analyses [d]							
GLD use	294	6.9	(6.8 to 7.0)	-0.12	(-0.18 to -0.06) *	0.12	(0.02 to 0.21) *
BMI at baseline [e]	123	6.8	(6.6 to 6.9)	-0.15	(-0.24 to -0.05) *	0.15	(0.03 to 0.28) *
Hb at baseline [e]	53	6.9	(6.6 to 7.1)	-0.10	(-0.26 to 0.05)	0.39	(0.18 to 0.60) *

GLD: glucose lowering drug; CRC: colorectal cancer; BMI: body mass index; Hb: haemoglobin; 95% CI: 95% confidence interval. [a] Crude model included: only continuous variables for time pre and post CRC diagnosis, to give the baseline HbA_{1c} for the specific group of patients. [b] Full model included: continuous variables for time pre and post CRC diagnosis, as well as age at CRC diagnosis, sex, period of CRC diagnosis (year of baseline), stage of cancer, administration of surgery, radiotherapy (only for rectal cancer) and/or chemotherapy and duration of glucose lowering drug use; [c] For the adjusted model the * reflects a $p<0.05$, while the ** reflects a $p<0.0001$; [d] The sensitivity analyses were performed for subselections of patients and the adjusted models were adjusted for the standard variables of the full model and the use of GLD, BMI at baseline and Hb at baseline, respectively. [e] BMI and Hb at diagnosis were defined as BMI and Hb measures within the 6 months around CRC diagnosis and only in the adjusted model additionally included as continuous variables.

Table 2. HbA_{1c}-values (%) at baseline and changes within the four years around cancer diagnosis (n=438).

		Crude linear model [a]		Adjusted linear model [b]			
		Baseline		Time pre diagnosis (years)		Time post diagnosis (years)	
	Patients	Estimate	(95% CI)	Estimate	(95% CI) [c]	Estimate	(95% CI) [c]
Rectal cancer							
All patients	144	7.1	(6.9 to 7.2)	-0.18	(-0.28 to -0.08) *	0.04	(-0.09 to 0.16)
Subgroup analyses							
Incident GLD users	73	6.8	(6.6 to 7.0)	-0.13	(-0.26 to 0.01)	0.06	(-0.14 to 0.25)
Insulin use prior to CRC	49	7.5	(7.2 to 7.7)	-0.32	(-0.48 to -0.17) *	0.00	(-0.22 to 0.23)
No insulin use prior to CRC	95	6.8	(6.7 to 7.0)	-0.09	(-0.22 to 0.04)	0.05	(-0.11 to 0.21)
Sensitivity analyses [d]							
GLD use	144	7.1	(6.9 to 7.2)	-0.18	(-0.28 to -0.08) *	0.04	(-0.09 to 0.17)
BMI at baseline [e]	51	6.8	(6.6 to 7.1)	-0.17	(-0.30 to -0.04) *	0.18	(-0.01 to 0.37)
Hb at baseline [e]	27	7.1	(6.8 to 7.4)	-0.06	(-0.23 to 0.10)	0.11	(-0.23 to 0.46)

GLD: glucose lowering drug; CRC: colorectal cancer; BMI: body mass index; Hb: haemoglobin; 95% CI: 95% confidence interval. [a] Crude model included: only continuous variables for time pre and post CRC diagnosis, to give the baseline HbA_{1c} for the specific group of patients. [b] Full model included: continuous variables for time pre and post CRC diagnosis, as well as age at CRC diagnosis, sex, period of CRC diagnosis (year of baseline), stage of cancer, administration of surgery, radiotherapy (only for rectal cancer) and/or chemotherapy and duration of glucose lowering drug use; [c] For the adjusted model the * reflects a $p<0.05$, while the ** reflects a $p<0.0001$; [d] The sensitivity analyses were performed for subselections of patients and the adjusted models were adjusted for the standard variables of the full model and the use of GLD, BMI at baseline and Hb at baseline, respectively. [e] BMI and Hb at diagnosis were defined as BMI and Hb measures within the 6 months around CRC diagnosis and only in the adjusted model additionally included as continuous variables.

0.10-0.40; 2.7 mmol/mol; p=0.001) (Table 2). Although in other sensitivity analyses the mean HbA_{1c} did not change tremendously, when adjusting for Hb at cancer diagnosis the mean HbA_{1c} after cancer diagnosis increased with 0.39% per year (95% CI 0.18 to 0.60; 4.2 mmol/mol; n=53; p=0.0006). In patients with stage IV CC, the mean HbA_{1c} decreased with 0.17% (95% CI 0.29-0.05; 1.9 mmol/mol; p<0.0001; not shown) per year before cancer diagnosis, while after cancer diagnosis the mean HbA_{1c} did not change (0.03%; 95% CI -0.25 to 0.31; 0.3 mmol/mol; p=0.8; not shown).

Rectal cancer

For RC patients the crude linear model had an intercept, the estimate for HbA_{1c} at cancer diagnosis, of 7.1% (53.5 mmol/mol) (Table 2). Before cancer diagnosis the mean HbA_{1c} decreased with 0.18% per year (95% CI 0.08 to 0.28; 2.0 mmol/mol; p=0.0006), whereas per year after cancer diagnosis the mean HbA_{1c} changed not-significantly with +0.04% (95% CI -0.09 to 0.16; 0.4 mmol/mol; p=0.59). Among subgroups, the effects of time in relation to cancer diagnosis on HbA_{1c} were less clear for incident GLD users, with a decrease in mean HbA_{1c} of 0.13% per year (95% CI -0.01 to 0.26; 1.4 mmol/mol; p=0.07) before cancer diagnosis and a still non-significant change in mean HbA_{1c} of 0.06% per year (95% CI -0.14 to 0.25; 0.6 mmol/mol; p=0.56) after cancer diagnosis. Among insulin users the mean HbA_{1c} decreased with 0.32% per year (95% CI 0.17 to 0.48; 3.5 mmol/mol; p=0.0001) before cancer diagnosis. After adjusting for baseline BMI, mean HbA_{1c} increased with 0.18% per year (95% CI -0.01 to 0.37; 2.0 mmol/mol; p=0.07) (Table 2). In patients with stage IV RC, the mean HbA_{1c} did not change before cancer diagnosis (-0.02%; 95% CI -0.30 to 0.27; 0.2 mmol/mol; p=0.9; not shown), while after cancer diagnosis the mean HbA_{1c} decreased sharply, although this was not significant (-0.26%; 95% CI -0.97 to 0.44; 2.9 mmol/mol; p=0.4; not shown).

Discussion

This population based study revealed that among CC and RC patients that used GLDs more than two years prior to cancer diagnosis, mean HbA_{1c} levels decreased from two years before cancer diagnosis till cancer diagnosis with 0.1%-0.2% (1 to 2 mmol/mol) per year. After the diagnosis of cancer, only among CC patients, mean HbA_{1c} levels increased statistically significant with 0.1% (1 mmol/mol) per year within the two years after cancer diagnosis and thus returned to the levels as before. The effects seen both pre and post cancer diagnosis were more pronounced in patients with proximal colon tumours and users of anti-anaemic preparations before the diagnosis of CC.

For the decrease of HbA_{1c} before the diagnosis of cancer various hypotheses could be given, regarding both direct and indirect effects of the tumour on glucose metabolism in individuals with diabetes. Compared with normal cells, cancer cells use a disproportional share of the nutrients in their environment, partly because they metabolize glucose by aerobic glycolysis, i.e. the Warburg effect[24]. Since this pathway of obtaining energy is very inefficient, cancer cells need more glucose for the same amount of Adenosine triphosphate (ATP), the principal molecule that drives all energy-dependent cellular processes[24]. The abnormal metabolism due to the tumour and the reduced intake of food often observed in patients with cancer might cause cancer cachexia, since they result in a negative protein and energy balance with loss of adipose tissue, skeletal muscle and weight loss[25]. Indirectly this may all lower the glucose levels and as a result the levels of HbA_{1c}.

Studies on weight changes before the diagnosis of cancer are rare, but that weight loss is common among CRC patients is well known[26,27]. Moreover, an older study showed that the achievement of modest weight loss of ±10 kg in one year through a behavioural weight loss programme was associated with reductions in HbA_{1c} of 1.1%[28]. Nevertheless, the weight loss of ±10 kg as a result of cancer might have a totally different impact on HbA_{1c}-values compared with the weight loss among individuals with diabetes involved in a weight loss programme. Baseline BMI was missing for 60% of the patients, although this was rather high, this seems to be at random, because data from clinical laboratories was missing for geographical regions within the cohort and reflects no specific patient selection. However, the lack of longitudinal data for BMI is an important limitation in our study, future studies should investigate the impact of weight loss instead of baseline weight on the decrease in HbA_{1c} in cancer patients.

After cancer diagnosis, HbA_{1c} was increasing and returning to comparable levels as seen 2 years before cancer diagnosis. This rapid increase might be the result of patients returning to their normal food intake and lifestyle habits. Also, the natural course of diabetes has been described, showing an HbA_{1c} increase per year of 0.05% (0.5 mmol/mol)[29]. Although we hypothesised that surgery and the administration of chemotherapy would result in increased HbA_{1c} levels[30,31], HbA_{1c} over time was not different in the different treatment groups. On the other hand, the administration of chemotherapy might indirectly result in decreased HbA_{1c} levels, because the important side effect of chemotherapy, the loss of appetite, might lower the glucose levels[32]. Thus, the administration of chemotherapy is hypothesised to result in decreased as well as increased HbA_{1c}-levels and together the net result on HbA_{1c} can be zero.

In our study, patients with CC and RC were different from one another with regard to their HbA_{1c} trajectory, as well as with regard to the number of users of insulin and anti-anaemic preparations, the age distribution and the proportion of males. After adjusting for these baseline differences, the effects among both tumour types seemed more comparable.
CC patients who had a proximal colon tumour or used anti-anaemic preparations before cancer diagnosis had a more profound decrease in HbA_{1c} pre-cancer diagnosis. In line with the potential correlation between proximal colon tumours and anaemia in our study, a study found that the prevalence of anaemia diminished gradually as the location of the tumour was more distal towards the rectum, prevalence percentages were 68%, 40% and 30% for proximal colon, distal colon and RC, respectively[33]. Since HbA_{1c} levels reflect changes in glucose during the lifespan of an erythrocyte, changes in this lifespan can affect HbA_{1c}. An increase in the mean age of erythrocytes will increase HbA_{1c}, while rapid red cell turnover leads to a greater proportion of younger red cells and falsely low HbA_{1c} levels. Haemolysis, anaemia, iron, vitamin B12, or folate deficiency, or the treatments for these, all will be able to influence the levels of HbA_{1c}[16]. Interestingly, anaemia and iron deficiency are frequently present in patients with CRC, according to one study, in respectively 35% and 52% of the CRC patients[17]. The observed decrease and increase of HbA_{1c} in this study might just reflect the effects of these factors on HbA_{1c}, while the actual glucose metabolism does not change. In the sub analysis in which patients who were dispensed an anti-anaemic treatment before cancer diagnosis were excluded, the effect of time on HbA_{1c} almost disappeared, which supports the hypothesis that HbA_{1c} is not a valid measure in patients treated for anaemia. Accordingly, it would be of interest to see the change in HbA_{1c} in light of the change in Hb, unfortunately, in our analyses we were not able to investigate this, because of low patients numbers when analysing the Hb longitudinally as well. For this study we used data from daily practice. As a consequence of this, evaluating the changes in glucose levels due to cancer would not have given reliable results, since the decision of the physician to measure the bloodglucose is already biased.

In summary, this study revealed that HbA_{1c}-values change around the diagnosis of CC and RC, with levels decreasing from two years before cancer diagnosis till cancer diagnosis for both cancer types and increasing within the two years after cancer for CC. The most profound HbA_{1c} changes were seen for those patients who had a proximal colon tumour or used anti-anaemic preparations before cancer diagnosis. Thus, the observed decrease and increase of HbA_{1c} in this study might just reflect the effects of anaemia, iron deficiency and the treatment for these on HbA_{1c}, while the actual glucose metabolism did not change. This study addressed

that among individuals that use GLDs and have beside a decrease in HbA_{1c} also anaemia and weight loss, physicians should be aware of the possible presence of cancer. In addition, physicians should be aware that the HbA_{1c} measure to monitor glycaemic control might be an inappropriate test in those with an (un) diagnosed cancer and thus need to be careful when stopping GLDs because of improved levels of HbA_{1c}. Nevertheless, against our hypothesis, the presence of cancer did not result in worse glycaemic control in our studied population.

References

1. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2011;26(11):863-76.
2. Kramer HU, Schottker B, Raum E, Brenner H. Type 2 diabetes mellitus and colorectal cancer: meta-analysis on sex-specific differences. Eur J Cancer. 2012;48(9):1269-82.
3. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679-87.
4. Bella F, Minicozzi P, Giacomin A, Crocetti E, Federico M, Ponz de Leon M, et al. Impact of diabetes on overall and cancer-specific mortality in colorectal cancer patients. J Cancer Res Clin Oncol. 2013.
5. Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, 3rd, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003;21(3):433-40.
6. Stein KB, Snyder CF, Barone BB, Yeh HC, Peairs KS, Derr RL, et al. Colorectal cancer outcomes, recurrence, and complications in persons with and without diabetes mellitus: a systematic review and meta-analysis. Dig Dis Sci. 2010;55(7):1839-51.
7. van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. Diabetologia. 2012;55(8):2163-72.
8. Dehal AN, Newton CC, Jacobs EJ, Patel AV, Gapstur SM, Campbell PT. Impact of diabetes mellitus and insulin use on survival after colorectal cancer diagnosis: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol. 2011;30(1):53-9.
9. Polednak AP. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: a population-based study. Cancer Detect Prev. 2006;30(5):466-72.
10. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
11. Wermeling PR, Gorter KJ, Stellato RK, de Wit GA, Beulens JW, Rutten GE. Effectiveness and cost-effectiveness of 3-monthly versus 6-monthly monitoring of well-controlled type 2 diabetes patients: a pragmatic randomised controlled patient-preference equivalence trial in primary care (EFFIMODI study). Diabetes Obes Metab. 2014;16(9):841-9.
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1:S62-9.
13. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. J Diabetes. 2009;1(1):9-17.
14. Ludwig H, Muldur E, Endler G, Hubl W. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol. 2013;24(7):1886-92.
15. Nicholas J, Charlton J, Dregan A, Gulliford MC. Recent HbA_{1c} values and mortality risk in type 2 diabetes. population-based case-control study. PLoS One. 2013;8(7):e68008.
16. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet. 2010;375(9713):481-9.
17. Carson AP, Fox CS, McGuire DK, Levitan EB, Laclaustra M, Mann DM, et al. Low hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. Circ Cardiovasc Qual Outcomes. 2010;3(6):661-7.
18. Gerstein HC, Swedberg K, Carlsson J, McMurray JJ, Michelson EL, Olofsson B, et al. The hemoglobin A1c level as a progressive risk factor for cardiovascular death, hospitalization for heart failure, or death in patients with chronic heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Arch Intern Med. 2008;168(15):1699-704.
19. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395-404.
20. World Health Organization. Collaborating Centre for Drug Statistics Methodology - ATC/DDD index. Accessed at www.whocc.no/atc_ddd_index, 2014.

21. Kaelin WG, Jr., Thompson CB. Q&A: Cancer: clues from cell metabolism. Nature. 2010;465(7298):562-4.

22. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153-66.

23. Hamilton W, Round A, Sharp D, Peters TJ. Clinical features of colorectal cancer before diagnosis: a population-based case-control study. Br J Cancer. 2005;93(4):399-405.

24. Ford AC, Veldhuyzen van Zanten SJ, Rodgers CC, Talley NJ, Vakil NB, Moayyedi P. Diagnostic utility of alarm features for colorectal cancer: systematic review and meta-analysis. Gut. 2008;57(11):1545-53.

25. Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D. Long-term effects of modest weight loss in type II diabetic patients. Arch Intern Med. 1987;147(10):1749-53.

26. Lind M, Pivodic A, Cea-Soriano L, Nerman O, Pehrsson NG, Garcia-Rodriguez LA. Changes in HbA_{1c} and frequency of measuring HbA_{1c} and adjusting glucose-lowering medications in the 10 years following diagnosis of type 2 diabetes: a population-based study in the UK. Diabetologia. 2014;57(8):1586-94.

27. McConnell YJ, Johnson PM, Porter GA. Surgical site infections following colorectal surgery in patients with diabetes: association with postoperative hyperglycemia. J Gastrointest Surg. 2009;13(3):508-15.

28. Harris D, Barts A, Connors J, Dahl M, Elliott T, Kong J, et al. Glucocorticoid-induced hyperglycemia is prevalent and unpredictable for patients undergoing cancer therapy: an observational cohort study. Curr Oncol. 2013;20(6):e532-8.

29. Sanchez-Lara K, Ugalde-Morales E, Motola-Kuba D, Green D. Gastrointestinal symptoms and weight loss in cancer patients receiving chemotherapy. Br J Nutr. 2013;109(5):894-7.

30. Edna TH, Karlsen V, Jullumstro E, Lydersen S. Prevalence of anaemia at diagnosis of colorectal cancer: assessment of associated risk factors. Hepatogastroenterology. 2012;59(115):713-6.

9

Impact of cancer on adherence to glucose lowering drugs in individuals with diabetes

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Abstract

Aims: Adherence to glucose lowering drugs (GLDs) is crucial for metabolic control and improving prognosis. Because a diagnosis of cancer might impact medication adherence, this study explored changes in adherence to GLDs following a cancer diagnosis.

Methods: All new users of GLDs between 1998 and 2011 who lived in the ECR-PHARMO catchment area were selected. Those with a primary cancer diagnosis during follow-up were considered cases and matched with eligible controls without cancer during follow-up. Medication Possession Ratio (MPR) was used as indicator for medication adherence. Segmented linear auto-regression analysis with interrupted time-series was used to assess changes in MPR for cases compared to controls (i.e. overall trend) due to (any) cancer diagnosis and specific cancer types.

Results: From the 52,228 GLDs users selected, 3,281 cases with cancer and 12,891 controls without cancer during follow-up were included in the study. In our analyses, before cancer diagnosis the MPR increased by 0.10% per month (95% CI 0.10% to 0.10%). Besides a significant drop in MPR at the time of cancer diagnosis of -6.3% (95% CI -6.5% to -6.0%), there was an ongoing, yet lower, monthly decline in MPR (-0.20%; 95% CI -0.21% to -0.20%) after cancer diagnosis. The largest drops in MPR at the time of cancer diagnosis, in the range of 12-15%, were seen among patients with stage IV disease and gastrointestinal or pulmonary cancers.

Conclusions: Our findings indicate a clear decline in adherence to GLDs following a cancer diagnosis. The reason for the decline in MPR needs to be further elucidated.

Introduction

Cancer patients with diabetes have a significantly higher overall mortality risk compared with patients without diabetes[1-3]. To understand the association between diabetes and cancer, the American Diabetes Association and American Cancer Society reviewed the state of science regarding this in 2010[4]. One of the key goals of the review was to gain a better understanding of whether diabetes influences cancer prognosis above and beyond the prognosis conferred by each disease independently. Since that report, most research has focussed on the influence of diabetes and glucose lowering drugs (GLDs) on outcomes after cancer diagnosis; on the contrary, cancer might affect outcomes associated with diabetes.

Achievement of normal or near normal glycaemia (HbA_{1c} goal of <7%; 53 mmol/mol[5]) among individuals with diabetes is strongly linked with medication adherence[6,7]. Overall, only 65%-85% of GLDs users are regarded as adherent[8,9]; this might decrease even more due to the diagnosis of cancer. If the presence of a cancer diagnosis can influence medication adherence among GLDs users, this could also affect HbA_{1c} levels leading to poor metabolic control, higher risk of diabetes complications and worse overall mortality. Today, only one – very recent – study has examined the impact of a cancer diagnosis on medication adherence. Among 509 individuals with diabetes, the diagnosis of breast cancer has been associated with a decline in medication adherence – measured with the medication possession ratio (MPR) – from 86% to 49%[10]. Although the investigators measured the MPR among those with breast cancer, the natural course of adherence to GLDs among diabetic patients without cancer is unknown. Therefore, we aimed to evaluate changes in adherence to GLDs due to a cancer diagnosis, taking into account the changes in adherence to GLDs among those without cancer.

Methods

Data sources

Data were obtained from the PHARMO Database Network and linked at the individual patient level to the Eindhoven Cancer Registry (ECR). The data covered a demographic region in the Southern part of the Netherlands, for approximately one million inhabitants. The construction and validity of the ECR-PHARMO cohort have been described elsewhere[11]. The PHARMO Database Network is a large, patient-centric data network including multiple linked observational databases designed for safety and outcomes research of drugs. For this study the community pharmacy (out-patient) database was used, which includes data on the dispensed drug, dispensing date, amount dispensed, and thus the duration of use could be calculated. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification[12]. The ECR, maintained by the Netherlands Comprehensive

Cancer Organisation (IKNL), records data on all patients newly diagnosed with cancer in the Southern part of the Netherlands, an area with 2.4 million inhabitants. Six pathology departments, 10 community hospitals, and two radiotherapy departments notify the registry. Trained registration clerks actively collect data on patient characteristics, cancer diagnosis, staging, and initial treatment from hospital medical records. Both the ECR and the PHARMO Database Network are recognised as high quality sources for epidemiological research that collect information in overlapping regions in the Netherlands for a period of at least 10 years[11].

Study population

The source population included all patients living in the geographical region of the ECR-PHARMO cohort and being aged over 30 years with a dispensing of GLDs (ATC code: A10) between January 1, 1998 and December 31, 2011 (n=81,928). From this source population, we selected incident users of GLDs who had two or more dispensings of GLDs preceded by a six-month period without any GLDs dispensing (n=52,228).

Users of GLDs with a primary diagnosis of any cancer (except non-melanoma skin cancer) were considered cases and the date of the first cancer diagnosis (i.e. a confirmed cancer by pathology) was set as the time of the event. Those GLDs users without a diagnosis of cancer were eligible as controls. By including controls we were able to account for the overall course (i.e. secular trend) in medication adherence seen in individuals with diabetes. Cases and controls were matched - with replacement and a maximum of 4 controls per case – on age (according to five-year age groups), sex, duration of follow-up (controls needed to have a similar or longer duration of follow-up than the total follow-up time for their cases), calendar year of first GLDs dispensing (according to two-year periods) and type of first dispensed GLDs (metformin monotherapy, sulfonylurea derivatives monotherapy, any insulin or other GLDs groups). Both the time till the diagnosis of cancer and the total time of follow-up for the cases was then set as the same time for their controls. Because controls did not have an 'actual' cancer diagnosis, we needed to define an index date for the controls. We assigned this as the date associated with the same duration of GLDs use at cancer diagnosis as for their case.

For the primary analysis we were interested in the change in medication adherence potentially associated with any cancer diagnosis, but also associated with one of the six most frequent cancer types/groups classified according to the International Classification of Diseases of Oncology (ICD-O): colorectal (C18-20), other gastro-

intestinal (C15-17, C21-C26; oesophageal, stomach, pancreas and liver), prostate (C61), breast (C50), pulmonary (C33-34, C45) and urinary (C64-68) cancer[13].

Drug episodes for measuring medication adherence

For each oral drug dispensing (i.e. except insulin: ATC-code A10A[12]) the duration of use was calculated by dividing the number of tablets dispensed by the number of tablets to be used per day, as defined in the outpatient pharmacy database. For insulin, the duration of use is not often registered in the pharmacy. The intended period of use for which insulin was dispensed was set to 90 days when the duration of use was missing or considered unlikely.

All dispensings for GLDs, regardless of type, were converted into episodes of uninterrupted use. For each dispensing, the duration of use was calculated and converted into episodes of consecutive use based on the method of Catalan[14]. In this method, the time span was the date of the first dispensing until the end date of the final dispensing together with the permissible gap. This gap was determined to be either half the period of the given dispensing or seven days, whichever was greater. Because many patients resumed the same treatment within two months of the end of the previous episode, we expanded the permissible gap between drug dispensings of the same drug with an additional 45 days.

We used the Medication Possession Ratio (MPR) as an indicator for medication adherence, representing the amount of medication patients had in possession over a certain time period. Thus, a 10% decline in MPR translates to a difference of 3 days in a 30 day month that is not covered by the use of GLDs due to the cancer diagnosis. The MPR was calculated every month for both cases and controls by dividing the cumulative days of drug exposure by the total number of days in that time window[15]. Lastly, for every month (i.e. every time window) the MPR for cases was compared with the MPR for matched controls, these controls represented the overall trend among individuals with diabetes but without cancer. Thus, the impact of cancer on MPR for cases was set against this background trend.

Statistical analyses

Differences in demographic and clinical characteristics between users of GLDs with any cancer and their controls were analysed using chi square and the t-test where applicable.

We used the method for interrupted time-series analysis[16], with monthly time-windows for the MPR in cases and controls. A segmented linear auto-regression analysis was used to statistically measure the changes in MPR in intercept and slope in the post-cancer period compared to the pre-cancer period. The regression model used to fit our data included a continuous variable for time from first dispensing of GLDs until the end of that time window, a binary variable for time

occurring before or after the diagnosis of cancer, and a continuous variable for time after cancer. The parameter estimates for the binary variable as well as for the variable for the time after cancer are of main interest, whereas the parameter for time from first dispensing of GLDs controls for the overall trend in MPR regardless of a cancer diagnosis. We calculated the Durbin-Watson statistic to test for the serial autocorrelation of the error terms in the regression models. We corrected for any autocorrelation according to the order (number of lags), which was given by the Durbin-Watson statistic to be significant. All final models had a Durbin-Watson statistic value close to the preferred value of 2[17]. A p-value <0.05 was considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute, Cary, US).

Regression analyses were performed for all cancers combined and for the previously mentioned cancer types separately. In addition, we stratified the analyses for the TNM stage of cancer as well as for the cancer treatment received, to explore their effects on the medication adherence in our study population. Additional subgroup analyses were performed, in which we stratified according to age groups (<60, ≥60 and <70, ≥70) and according to the type of GLDs used at cancer diagnosis, because a cancer diagnosis might impact adherence different in these subgroups.
Because patients with a recent start of GLDs might differ in their medication adherence compared to long time users, users of GLDs who started using GLDs in the 6 months prior to cancer diagnosis were excluded in a sensitivity analyses. To evaluate whether medication adherence was influenced directly by mortality, a sensitivity analyses was performed in which only those patients who died during follow-up were included.

Results

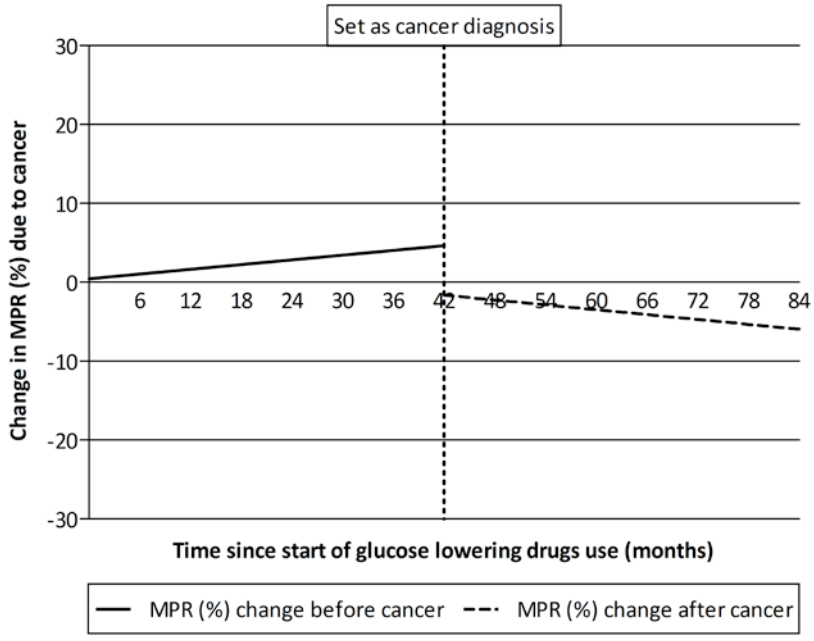
From the ECR-PHARMO cohort, 3,281 cases with cancer and 12,891 controls without cancer were selected (Table 1). The mean (standard deviation (SD)) age at the start of GLDs use was 67.6 (9.7) years for cases and 67.7 (9.8) years for controls (p=0.3). Most patients started with their GLDs use before 2005. Time between the start of GLDs use and the date of cancer diagnosis (or index date for controls) was 3.7 (3.0) years for both groups and the total duration of follow-up was 6.6 (3.5) years for cases and 6.5 (3.5) years for controls (Table 1). Before cancer diagnosis or index date for the controls, 33% of the cases stopped with the use of GLDs and among the controls the number of patients that used insulin or combination treatment increased (Table 1).

In our analyses, before cancer diagnosis the MPR increased by 0.10% per month

(95% CI 0.10% to 0.10%) (Table 2, Figure 1). Besides a significant drop in MPR at the time of cancer diagnosis of -6.3% (95% CI -6.5% to -6.0%), there was an ongoing, yet lower monthly decline in MPR (-0.20%; 95% CI -0.21% to -0.20%) after cancer diagnosis, both indicating a clear decline in medication adherence because of cancer.

When we stratified the analysis for the type of cancer, different effects were seen for the various tumour types (Table 2, Figure 2). While no important decline in MPR was seen at the time of diagnosis for prostate (2.1%; 95% CI 1.4% to 2.8%) and breast cancer (-0.5%; 95% CI -1.2% to 0.3%), large drops were seen among patients with oesophageal, stomach, pancreas or liver cancer (-12.5%; 95% CI -13.4% to -11.6%) and pulmonary cancers (-15.2%; 95% CI -16.0% to -14.4%) (Figure 2). Among those patients with large drops, the MPR after cancer diagnosis decreased approximately 0.5% monthly, indicating ongoing declining medication adherence in cases (oesophageal, stomach, pancreas or liver cancer -0.45%; 95%

Figure 1. Change in MPR (%) due to cancer, in which the diagnosis of any cancer was set on 42 months (3.5 years).*



*The change in MPR for cases was set against the background trend, i.e. the overall trend in MPR among individuals with diabetes/ the controls.

Table 1 Characteristics of study population (n=16,172).

	Users of GLDs who developed cancer (n=3,281)		Matched users of GLDs without cancer (n=12,891)		
	n	(%)	n	(%)	p-value
Patient characteristics					
Age at first GLDs dispensing (years; Mean (SD))	67.5	(±9.7)	67.7	(±9.8)	0.3
Male	1839	(56)	7218	(56)	1.0
Year of initiation of GLDs use					
1998-2001	1030	(32)	4030	(31)	
2002-2005	1286	(39)	5059	(39)	
2006-2009	860	(26)	3386	(27)	
2010-2011	105	(13)	416	(3)	1.0
Use of GLDs					
At start of use of GLDs					
Metformin monotherapy	1627	(50)	6442	(50)	
Sulfonylurea derivatives monotherapy	1308	(40)	5163	(40)	
Insulin (monotherapy or combination with)	199	(6)	742	(6)	
Other GLDs	147	(4)	544	(4)	0.8
At cancer diagnosis/index date					
Metformin monotherapy	836	(25)	4144	(32)	
Sulfonylurea derivatives monotherapy	826	(25)	3434	(27)	
Combination of metformin and sulfonylurea derivatives	155	(5)	1032	(8)	
Insulin (monotherapy or combination with)	280	(9)	1438	(11)	
Other GLDs	112	(3)	620	(5)	
No use of GLDs	1072	(33)	2223	(17)	<0.0001
Cancer					
Specific types of cancer					
Colorectal cancer	549	(17)	n.a.		
Oesophageal, stomach, pancreas or liver cancer	387	(12)			
Prostate cancer	377	(11)			
Breast cancer	415	(13)			
Pulmonary cancers	425	(13)			
Urinary cancer	390	(12)			
Other types of cancer	738	(22)			
Time between GLDs start and cancer/index date (years; means (SD))	3.7	(±3.0)	3.7	(±3.0)	0.8
TNM stage					
Non-invasive	249	(8)	n.a.		
I	679	(21)			
II	972	(20)			
III	498	(15)			
IV	612	(19)			
Unknown	571	(17)			
Received cancer treatment					
Surgery	1725	(53)	n.a.		
Chemotherapy	719	(22)			
Radiotherapy	827	(25)			

GLDs: glucose lowering drugs; SD: standard deviation. Index date: Because controls did not have an 'actual' cancer diagnosis, we needed to define an index date for the controls. We assigned this as the date associated with the same duration of GLDs use at cancer diagnosis as for their case.

Table 1 Characteristics of study population (n=16,172) (Continued).

	Users of GLDs who developed cancer (n=3,281)		Matched users of GLDs without cancer (n=12,891)		
	n	(%)	n	(%)	p-value
Follow-up					
Duration of follow-up (years; means (SD))	6.6	(±3.5)	6.5	(±3.5)	0.5
End of follow-up					
Death	1189	(36)	n.a.		
Loss to follow-up	42	(1)			
End of follow-up	2050	(63)			

GLDs: glucose lowering drugs; SD: standard deviation.

CI -0.47% to -0.42%; pulmonary cancers -0.54%; 95% CI -0.56% to -0.52%). In patients with oesophageal, stomach, pancreas or liver cancer, the largest declines were seen for liver and oesophageal cancer (-35.3%; 95% CI -39.1 to -31.5 and -19.2%; 95% CI -20.9% to 17.4%; respectively) (Appendix 1). Within the group of pulmonary cancers both small cell and non-small cell lung cancer had comparable declines in MPR (Appendix 1). However, for each extra month after cancer diagnosis, the MPR declined further with almost 1% each month among pancreas and small cell lung cancer (-0.97%; 95% CI -1.01% to -0.93% and -0.89%; 95% CI -0.95% to -0.84%, respectively) (Appendix 1). When comparing colon and rectal cancer patients, the degree of drop in MPR at cancer diagnosis remained for colon cancer patients, whereas it disappeared for rectal cancer patients (Appendix 1).

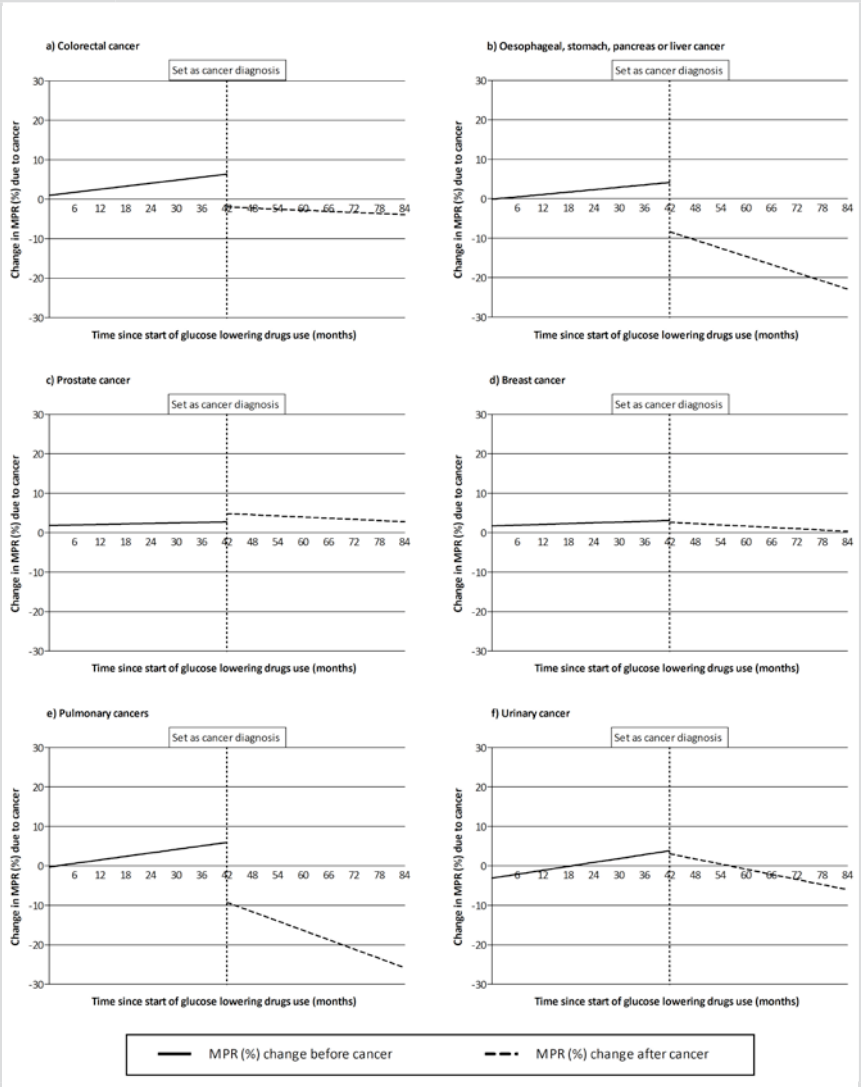
The higher the TNM stage, the greater the observed decline in medication adherence at cancer diagnosis (Table 3). Among patients with stage IV disease, the drop in MPR was -10.7% (95% CI -11.3% to -10.1%), while each extra month after cancer diagnosis the MPR declined an additional -0.64% (95% CI -0.66% to -0.62%). Although no effect modification by chemotherapy or radiotherapy administration was seen, cancer patients who did not receive surgery had a more pronounced drop in MPR at cancer diagnosis (-10.8%; 95% CI -11.2% to -10.4%), compared to those who did receive surgery (-2.8%; 95% CI -3.1% to -2.4%; Table 3). The impact of cancer on medication adherence was significant for all age groups, but with larger decreases in MPR with increasing age. Moreover, after cancer diagnosis, the decline in MPR was larger with increasing age (Table 3). The impact of a cancer diagnosis on MPR was most apparent among patients that used sulfonylurea derivatives in combination with metformin and among patients that used insulin as monotherapy or combination therapy at cancer diagnosis (Table 3). The inclusion of only long time GLDs users or the inclusion of those who died during follow-up resulted in comparable estimates for the MPR at cancer diagnosis and for the monthly MPR change after cancer diagnosis (Table 3).

Table 2. Medication adherence, change in MPR (%) during follow-up due to the diagnosis of cancer.

		Intercept at first drug dispensing		Time before cancer/index date (per month)		Intercept at cancer diagnosis		Time after cancer (per month)	
	Ncases/Ncontrols	MPR Δ	95% CI	MPR Δ	95% CI	MPR Δ	95% CI	MPR Δ	95% CI
All cancers									
Any cancer	3281/12891	0.4	(0.1 to 0.8) *	0.10	(0.10 to 0.10) **	-6.3	(-6.5 to -6.0) **	-0.20	(-0.21 to -0.20) **
Stratified for type of cancer									
Colorectal cancer	549/2154	1.0	(0.1 to 1.9) *	0.13	(0.12 to 0.14) **	-8.3	(-9.0 to -7.7) **	-0.17	(-0.19 to -0.16) **
Oesophageal, stomach, pancreas or liver cancer	387/1526	-0.1	(-1.3 to 1.0)	0.10	(0.09 to 0.11) **	-12.5	(-13.4 to -11.6) **	-0.45	(-0.47 to -0.42) **
Prostate cancer	377/1463	1.8	(0.8 to 2.9) *	0.02	(0.01 to 0.03) *	2.1	(1.4 to 2.8) **	-0.07	(-0.09 to -0.05) **
Breast cancer	415/1617	1.7	(0.7 to 2.8) *	0.03	(0.02 to 0.04) **	-0.5	(-1.2 to 0.3)	-0.09	(-0.10 to -0.07) **
Pulmonary cancers	425/1694	-0.3	(-1.2 to 0.7)	0.15	(0.14 to 0.16) **	-15.2	(-16.0 to -14.4) **	-0.54	(-0.56 to -0.52) **
Urinary cancer	390/1528	-3.1	(-4.2 to -2.0) **	0.17	(0.15 to 0.18) **	-0.8	(-1.5 to -0.1) *	-0.38	(-0.40 to -0.36) **

GLDs: glucose lowering drugs; MPR Δ: absolute change in medication possession ratio(%); Index date: Because controls did not have an 'actual' cancer diagnosis, we needed to define an index date for the controls. We assigned this as the date associated with the same duration of GLDs use at cancer diagnosis as for their case; * p<0.05; ** p<0.0001.

Figure 2. Change in MPR (%) due the different cancer types, in which the diagnosis of cancer was set on 42 months (3.5 years).*



*The change in MPR for cases was set against the background trend, i.e. the overall trend in MPR among individuals with diabetes/ the controls.

Table 3. Subgroup analyses of medication adherence, change in MPR (%) during follow-up due to the diagnosis of cancer.

		Intercept at first drug dispensing		Time before cancer/index date (per month)		Intercept at cancer diagnosis		Time after cancer (per month)	
	Ncases/Ncontrols	MPR Δ	95% CI	MPR Δ	95% CI	MPR Δ	95% CI	MPR Δ	95% CI
TNM stage									
I	679/2677	-0.5	(-1.6 to 0.6)	0.07	(0.07 to 0.08) **	0.3	(-0.2 to 0.8)	-0.10	(-0.11 to -0.08) **
II	972/2610	1.7	(0.6 to 2.7) **	0.08	(0.07 to 0.09) **	-3.2	(-3.7 to -2.7) **	-0.09	(-0.11 to -0.08) **
III	498/1939	-2.2	(-3.4 to -0.9) **	0.16	(0.15 to 0.17) **	-5.8	(-6.4 to -5.2) **	-0.32	(-0.34 to -0.31) **
IV	612/2439	-0.6	(-1.8 to 0.5)	0.15	(0.14 to 0.16) **	-10.7	(-11.3 to -10.1) **	-0.64	(-0.66 to -0.62) **
Initial cancer treatment									
Surgery	1725/6760	0.0	(-0.5 to 0.6)	0.09	(0.08 to 0.09) **	-2.8	(-3.1 to -2.4) **	-0.16	(-0.17 to -0.16) **
No surgery	1556/6131	0.7	(0.2 to 1.3) **	0.11	(0.11 to 0.12) **	-10.8	(-11.2 to -10.4) **	-0.29	(-0.30 to -0.28) **
Chemotherapy	719/2848	-0.1	(-0.9 to 0.7)	0.11	(0.10 to 0.12) **	-5.2	(-5.7 to -4.6) **	-0.39	(-0.40 to -0.37) **
No chemotherapy	2562/10043	0.6	(0.2 to 1.0) **	0.10	(0.09 to 0.10) **	-6.4	(-6.7 to -6.1) **	-0.17	(-0.18 to -0.16) **
Radiotherapy	827/3230	0.4	(-0.3 to 1.2)	0.07	(0.07 to 0.08) **	-3.8	(-4.3 to -3.3) **	-0.15	(-0.16 to -0.13) **
No radiotherapy	2454/9661	0.4	(-0.1 to 0.9)	0.11	(0.10 to 0.11) **	-7.2	(-7.5 to -6.9) **	-0.23	(-0.24 to -0.22) **
Age at start of GLDs use									
<60 years	654/2573	0.6	(-0.1 to 1.2)	0.01	(0.00 to 0.02) *	-4.2	(-4.8 to -3.7) **	-0.16	(-0.18 to -0.15) **
≥60 and <70 years	1163/4611	0.5	(0.1 to 1.0) *	0.12	(0.11 to 0.12) **	-6.3	(-6.8 to -5.9) **	-0.21	(-0.22 to -0.20) **
≥70 years	1464/5707	0.6	(0.1 to 1.1) *	0.17	(0.16 to 0.17) **	-8.3	(-8.7 to -7.8) **	-0.27	(-0.28 to -0.26) **
Type of GLDs used at cancer diagnosis [a]									
Monotherapy metformin	836/3304	-0.1	(-0.7 to 0.5)	0.27	(0.27 to 0.28) **	-2.4	(-2.9 to -1.9) **	-0.72	(-0.73 to -0.70) **
Monotherapy sulfonylurea derivatives	826/3258	2.7	(2.2 to 3.3) **	0.26	(0.25 to 0.27) **	-8.8	(-9.3 to -8.3) **	-0.49	(-0.50 to -0.47) **
Insulin	280/1100	2.1	(1.3 to 3.0) **	0.24	(0.23 to 0.25) **	-6.1	(-7.1 to -5.2) **	-0.76	(-0.79 to -0.73) **
Metformin and sulfonylurea derivatives	155/616	5.5	(4.3 to 6.7) **	0.16	(0.15 to 0.18) **	-19.5	(-20.7 to -18.3) **	-0.62	(-0.65 to -0.58) **
Other GLDs	112/445	1.4	(-0.1 to 2.8)	0.12	(0.10 to 0.14) **	-2.6	(-4.1 to -1.1) *	-0.54	(-0.58 to -0.50) **
No use of GLDs	1072/4168	-1.5	(-2.1 to -1.0) **	-0.15	(-0.16 to -0.15) **	-3.0	(-3.5 to -2.6) **	0.26	(0.25 to 0.27) **
Sensitivity analyses									
Exclusion of users of GLDs < 6 months[b]	2857/11215	-0.2	(-0.7 to 0.3)	0.11	(0.11 to 0.12) **	-5.1	(-5.4 to -4.9) **	-0.24	(-0.25 to -0.23) **
GLDs users who died during follow-up[c]	1189/4739	-1.7	(-2.6 to -0.9) **	0.23	(0.22 to 0.24) **	-5.3	(-5.8 to -4.9) **	-0.34	(-0.35 to -0.32) **

GLDs: glucose lowering drugs; MPR Δ: absolute change in medication possession ratio(%); Index date: Because controls did not have an 'actual' cancer diagnosis, we needed to define an index date for the controls. We assigned this as the date associated with the same duration of GLDs use at cancer diagnosis as for their case. [a] We performed subgroup analyses in which the type of GLDs used at cancer diagnosis of the case determined the subgroup; [b] In this sensitivity analysis GLDs users that started their used within the 6 months prior to cancer diagnosis were excluded; [c] In this sensitivity analysis, only GLDs users with a cancer diagnosis during follow-up that died during follow-up and their controls were included; * p<0.05; ** p<0.0001.

Discussion

This population-based study revealed that among new GLDs users, the diagnosis of cancer negatively influenced medication adherence, with a decrease in MPR of 6% at the time of cancer diagnosis. Importantly, the influence of cancer on GLDs adherence seemed to be influenced by the type of cancer, with more pronounced effects among patients with oesophageal, stomach, pancreas or liver cancer and pulmonary cancers. Also, more advanced cancer stages at diagnosis resulted in substantially lower MPRs at the time of cancer diagnosis.

In this study, the MPR drop of 6% at the time of any cancer diagnosis translates to a difference of 2 days in a month that is not covered by the use of GLDs due to the diagnosis of any cancer. The sensitivity of the MPR as an indicator for medication adherence has been assessed in many studies. In general, a MPR of over 80% is indicative of being adherent to the drug[15,18]. Consequently, a 20% MPR drop because of cancer would be considered the cut-off for an adherent compared to a non-adherent GLDs user. Based on these values, it may be that the overall decline of 6% we observed may not be considered clinically important. On the other hand, the decline in MPR observed in patients with more severe or advanced cancers may be considered clinically important.

Interestingly, previous studies showed that relatively small changes in MPR are associated with changes in metabolic control[6,7]. In one study, a statistically significant 48% decrease in the odds of poor glycaemic control (HbA_{1c} >8%) was found for each percentage increase in MPR (OR 0.5; 95% CI 0.4-0.6)[6]. A previous study showed that individuals with diabetes and recent HbA_{1c} values >9.0% (OR 1.5; 95% CI 1.3-1.7) had higher mortality compared to those with recent 'normal' HbA_{1c} values between 6.5% and 9%[19]. Thus, the drop in MPR observed among patients with cancer in our study might have negatively influenced survival via the mechanisms as mentioned-above and may (partly) explain the established association between diabetes, cancer and survival[1-3].

The diagnosis of prostate and breast cancer seemed to have no influence on medication adherence in GLDs users, which is the opposite of what was previously observed among 509 American breast cancer patients[10]. In this study, one year before the cancer diagnosis the MPR was 85% in these patients, while during the treatment period of cancer (cancer diagnosis until 210 days after) it declined to 49%[10]. Although this decline in MPR is remarkable, the absence of a control group without breast cancer and lack of information on drug duration are limitations of this study[10]. The control group is needed, because generally, the MPR does tend to decrease over time among users of GLDs. In one study, with most patients

having drug durations of <10 years, approximately two-thirds of the patients had a MPR under 65%[20].

In our study, among oesophageal, stomach, pancreas or liver cancer and pulmonary cancer, the impact of cancer on adherence was large. While it is indisputable that drops of around 15% in MPR have their influence on metabolic control and mortality, we need to understand how medication adherence among users of GLDs was particularly influenced by these types of cancer. Compared to the other types of cancer under study, these cancer types are associated with the worst prognosis and with the lowest rates of tumour resections[21]. The hypothesis that the prognosis of cancer is associated with medication adherence is strengthened by our results revealing that the TNM stage[22], which is the most important prognostic factor in cancer patients, also seems to be associated with medication adherence. Evidence suggests that medication adherence in users of GLDs seems to decrease following major life events or when people are under stress[9,23]. A diagnosis of stage IV disease, could be considered such a major life event. Users of GLDs with more lethal cancers might prioritize the fight against cancer over the effort required to have a good metabolic control for their diabetes. This 'life chaos' due to another disease was investigated among post-myocardial patients[24]. After adjusting for other potential factors associated with medication non-adherence, life chaos, according to questions whether they had a stable or organized life, was significantly associated with non-adherence to drugs for cardiovascular disease[24]. Lastly, the prognosis seemed to only partly explain the impact of cancer on medication adherence, because among oesophageal cancer patients (3-year survival of 17%[21]), the diagnosis of cancer had a stronger impact on medication adherence compared to patients with the most lethal form of cancer, pancreas cancer (3-year survival of 6%[21]). This difference may also be explained by symptoms of cancer that might result in intolerable intake of oral drugs, leading to discontinuation of GLDs therapy. In addition, the administration of chemotherapy might be expected to influence medication adherence, although this was not found in our subgroup analyses with patients who did or did not receive chemotherapy. In this study, the impact of a cancer diagnosis on adherence seemed to depend on the age at first use of GLDs and on the type of GLDs used at cancer diagnosis. Although we matched our cases and controls on these criteria, the age and the type of GLDs used, i.e. the complexity of the treatment scheme, remain important factors to consider when assessing medication adherence.

Among liver cancer patients (n=23), the diagnosis of cancer strongly influenced the MPR with a 35% decline at cancer diagnosis. The association between diabetes and liver cancer might reflect some degree of 'reverse causality', with liver cancer

itself or its related liver diseases (such as cirrhosis) leading to the onset of diabetes[25]. Once the tumour is removed, the insulin resistance might resolve, the physician stops the GLDs and the medication adherence declines. Moreover, metformin might be stopped, because it is contraindicated in patients with advanced liver diseases with associated cirrhosis, ascites, or encephalopathy[26]. Although the real risk is minimal[27], the potential of metformin to cause lactatic acidosis might lead physicians to withhold metformin in patients with advanced liver disease[26].

This study had many strengths, such as the inclusion of only new GLDs users with a known duration of GLDs use and the inclusion of a matched control group without cancer. However, pharmacy records provide no ascertainment whether patients were compliant with their medication prescriptions.
The MPR might be a good indicator for medication adherence, although the physician could have advised the patient to stop the treatment with GLDs, which could not be investigated. With our data, reasons for stopping their treatment for diabetes are unknown - is it because of frequent hypoglycaemic events due to cancer[28] or intolerable oral intake of drugs? Due to the lack of longitudinal HbA_{1c} data, we were not able to understand whether this might be explained by an improvement in metabolic control; however, our previous research (unpublished data) showed that HbA_{1c} values improved around the diagnosis of cancer. For this study we only had information from outpatient pharmacies, these do not include drugs used within the hospital or within nursing homes. This might have resulted in an overestimation of MPR decline. Another limitation was that for some patients we missed information on the duration of the dispensed insulin, we might have wrongly estimated these dispensings on 90 days.
The interrupted time series analysis is only valid to the extent that the cancer diagnosis was the only event that changed over time and the only event that was able to change the monthly calculated MPR[16]. In this study, the visit of an endocrinologist by the patient because of vague complaints of an undiagnosed cancer might be a competing event[29]. Moreover, missing dispensing data – for example because of hospitalisations –might falsely give the impression that medication adherence had fallen when in fact the data was simply missing. Because the database of PHARMO was linked to the ECR for the cancer incidence years 1998-2011, we were not able to exclude the users of GLDs with a previous or recent cancer diagnosis. Thus, at the start of use of GLDs the medication adherence might already have been influenced by cancer.

In summary, this study revealed that the medication adherence among users of GLDs was influenced by cancer diagnosis. Although the impact of cancer was

more pronounced among cancers with a worse prognosis and among those with more advanced TNM stages, the difference in prognosis associated with these cancers seemed to only partly explain the impact of cancer on medication adherence. The decline in adherence seen among users of GLDs with cancer might negatively impact survival and (partly) explain the established association between diabetes, cancer and survival[1-3]. In future studies, the reason for the decline in MPR needs to be further elucidated among the different cancer types - is it the patient who prioritizes the fight against cancer or the advice of the physician to stop the treatment?

References

1. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. Jama. 2008;300(23):2754-64.
2. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-32.
3. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
4. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.
5. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.
6. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal effects of medication nonadherence on glycemic control. Ann Pharmacother. 2014;48(5):562-70.
7. Lawrence DB, Ragucci KR, Long LB, Parris BS, Helfer LA. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. J Manag Care Pharm. 2006;12(6):466-71.
8. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. Clin Med Res. 2013;11(2):54-65.
9. Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. Am J Med. 2005;118 Suppl 5A:27S-34S.
10. Calip GS, Hubbard RA, Stergachis A, Malone KE, Gralow JR, Boudreau DM. Adherence to oral diabetes medications and glycemic control during and following breast cancer treatment. Pharmacoepidemiol Drug Saf. 2014.
11. van Herk-Sukel MP, van de Poll-Franse LV, Lemmens VE, Vreugdenhil G, Pruijt JF, Coebergh JW, et al. New opportunities for drug outcomes research in cancer patients: the linkage of the Eindhoven Cancer Registry and the PHARMO Record Linkage System. Eur J Cancer. 2010;46(2):395-404.
12. World Health Organization. Collaborating Centre for Drug Statistics Methodology - ATC/DDD index. Accessed at www.whocc.no/atc_ddd_index, 2014.
13. International Classification of Diseases of Oncology. Version 2013; first edition Geneva: WHO, 1976.
14. Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. Value Health. 2000;3(6):417-26.
15. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. Med Care. 2008;46(11):1125-33.
16. Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. Acad Pediatr. 2013;13(6 Suppl):S38-44.
17. Durbin J, Watson GS. Testing for serial correlation in least squares regression. II. Biometrika. 1951;38(1-2):159-78.
18. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin. 2009;25(9):2303-10.
19. Nicholas J, Charlton J, Dregan A, Gulliford MC. Recent HbA_{1c} values and mortality risk in type 2 diabetes. population-based case-control study. PLoS One. 2013;8(7):e68008.
20. Cohen HW, Shmukler C, Ullman R, Rivera CM, Walker EA. Measurements of medication adherence in diabetic patients with poorly controlled $HbA(_{1c})$. Diabet Med. 2010;27(2):210-6.
21. www.cijfersoverkanker.nl, Source Comprehensive Cancer Centre the Netherlands (IKNL), Accessed 07-07-2014.
22. Sobin LH, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. 7th Edition, Wiley Blackwell. 2009.
23. Peyrot M, McMurry JF, Jr., Kruger DF. A biopsychosocial model of glycemic control in diabetes: stress, coping and regimen adherence. J Health Soc Behav. 1999;40(2):141-58.
24. Zullig LL, Shaw RJ, Crowley MJ, Lindquist J, Grambow SC, Peterson E, et al. Association between perceived life chaos and medication adherence in a postmyocardial infarction population. Circ Cardiovasc Qual Outcomes. 2013;6(6):619-25.

25. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009;16(4):1103-23.

26. Glucophage (metformin hydrochloride) [package insert] Princeton, NJ: Bristol-Myers Squibb; 2009.

27. Misbin RI. The phantom of lactic acidosis due to metformin in patients with diabetes. Diabetes Care. 2004;27(7):1791-3.

28. Lopez JM, Annunziata K, Bailey RA, Rupnow MF, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of life, work productivity, and medication adherence. Patient Prefer Adherence. 2014;8:683-92.

29. Curkendall SM, Thomas N, Bell KF, Juneau PL, Weiss AJ. Predictors of medication adherence in patients with type 2 diabetes mellitus. Curr Med Res Opin. 2013;29(10):1275-86.

Appendix 1. Medication adherence, change in MPR (%) during follow-up due to the diagnosis of specific cancers.

		Intercept at first drug dispensing		Time before cancer/index date (per month)		Intercept at cancer diagnosis		Time after cancer (per month)	
	Ncases/Ncontrols	MPR Δ	95% CI	MPR Δ	95% CI	MPR Δ	95% CI	MPR Δ	95% CI
Colon	403/1590	1.9	(0.8 to 3.0)	0.11	(0.10 to 0.12) **	-11.7	(-12.5 to -11.0) **	-0.12	(-0.14 to -0.10) **
Rectal	146/564	-0.9	(-2.4 to 0.6)	0.18	(0.16 to 0.20) **	-0.1	(-1.3 to 1.1)	-0.33	(-0.36 to -0.30) **
Oesophagus	86/338	4.0	(2.0 to 6.0) **	0.05	(0.03 to 0.08) **	-19.2	(-20.9 to -17.4) **	-0.16	(-0.21 to -0.11) **
Stomach	69/271	-0.1	(-3.2 to 2.9)	0.15	(0.12 to 0.18) **	-11.2	(-13.2 to -9.2) **	-0.41	(-0.46 to -0.36) **
Pancreas	151/600	-1.5	(-3.3 to 0.3)	0.20	(0.17 to 0.22) **	-12.1	(-13.6 to -10.7) **	-0.97	(-1.01 to -0.93) **
Liver	23/88	-9.1	(-13.3 to -5.0) **	0.55	(0.50 to 0.60) **	-35.3	(-39.1 to -31.5) **	-0.33	(-0.42 to -0.25) **
Small cell lung	70/280	4.8	(2.8 to 6.8) **	0.03	(0.01 to 0.06) *	-15.9	(-17.9 to -14.0) **	-0.89	(-0.95 to -0.84) **
Non-small cell lung	281/1122	-0.3	(-1.2 to 0.7)	0.17	(0.16 to 0.18) **	-14.2	(-15.1 to -13.3) **	-0.64	(-0.67 to -0.61) **

GLDs: glucose lowering drugs; MPR Δ: absolute change in medication possession ratio(%); Index date: Because controls did not have an 'actual' cancer diagnosis, we needed to define an index date for the controls. We assigned this as the date associated with the same duration of GLDs use at cancer diagnosis as for their case; * p<0.05; ** p<0.0001.

10

Summary and general discussion

Summary of results

The research underlying this thesis aimed to understand how the combined effect of cancer and diabetes results in a worse mortality than the sum of the individual effects of cancer and diabetes.

The main objectives of the studies described in this thesis were:

- To assess the impact of diabetes on cancer treatment, cancer recurrence, cancer-specific and overall mortality in cancer patients.
- To assess whether, and to which extent, metformin, statin and aspirin use is associated with overall mortality in colorectal (CRC) patients with diabetes.
- To explore changes in glycaemic control and medication adherence among individuals with diabetes at the time of cancer diagnosis.

This thesis started with a general review in which we investigated the role of many factors that seem to be related with the association between diabetes, cancer and deteriorated outcomes among those with both diseases (**Chapter 2**). These factors are the presence of comorbidities and common risk factors, like ageing, smoking, unhealthy diet, obesity and physical inactivity. Moreover, newly designed studies should account for the stage of cancer and treatment differences and need to focus on tumour-related outcomes such as the risk of recurrence and cancer-specific survival. Thus, understanding the relationship between diabetes, cancer and prognosis is a major challenge, since new studies should adjust for the abundance of factors associated with diabetes, cancer and survival.

If diabetes affects the tumour characteristics at diagnosis, the administration of cancer treatment or cancer-specific outcomes, then diabetes may have a major impact on mortality among cancer patients. Within this thesis, the influence of diabetes on cancer stage at diagnosis, cancer recurrence, and survival of EC patients was investigated among endometrial cancer (EC) patients (**Chapter 3**). The population-based Eindhoven Cancer Registry (ECR) was used to select all 1,644 newly diagnosed EC patients between 2000-2008 with FIGO stage I-III. Patients with diabetes were diagnosed more often with a higher FIGO stage and had worse overall survival compared to patients without diabetes. Additionally, we collected data for a subgroup of 193 EC patients with diabetes and an age-matched sample of 195 EC patients without diabetes. In this subgroup, no association between diabetes status and recurrence rates was found. Moreover, after adjusting for a higher FIGO stage at diagnosis, no influence of diabetes on the EC-specific higher mortality was found.

Since the administration of cancer treatment impacts the chances of cure and survival, we investigated whether CRC patients with diabetes were treated less aggressively for their cancer compared to patients without diabetes (**Chapter 4**).

In this study we included 11,893 patients diagnosed with colon cancer and 5,277 with rectal cancer, of whom 1,711 (14%) and 609 (12%), respectively, had diabetes at the time of cancer diagnosis. Stage III colon cancer patients with diabetes received chemotherapy less often compared to those without diabetes (Odds Ratio (OR) 0.7; 95% CI 0.5-0.9; p=0.002). In addition, in both groups of patients the use of chemotherapy in patients with colon cancer increased sharply over time. Furthermore, the proportion of stage II/III rectal cancer patients with and without diabetes who received radiotherapy increased to a similar rate in recent years (81% and 87%, respectively). In conclusion, this study showed that the proportion of CRC patients with diabetes receiving radiotherapy and chemotherapy increased. Nevertheless, patients with diabetes still received chemotherapy less often than those without.

In the last decade the evidence accumulated that the association between diabetes and mortality among cancer patients varied with glucose lowering drugs (GLDs). In this thesis we aimed to assess whether CRC patients who used metformin or sulfonylurea derivatives after cancer diagnosis differed in the risk of overall mortality (**Chapter 5**). In our multivariate time-dependent Cox proportional hazards model, we observed that cumulative metformin exposure after CRC diagnosis was not associated with decreased overall mortality compared with sulfonylurea derivatives exposure. However, at the start of use of GLDs CRC patients using metformin already had a 59% lower hazard for overall mortality compared to those starting with sulfonylurea derivatives, suggesting that these users have favourable prognostic factors at the start of their drug use.
This thesis includes a published correspondence to the authors of another study on metformin, cancer and survival (**Chapter 6**) as it describes some methodological problems that arise in these pharmaco-epidemiological analyses. The results of the study by Margel et al.[1] – using Cox proportional hazards model with drug exposures after prostate cancer diagnosis as time-dependent covariates – might be affected by allocation bias (those prescribed and not prescribed the drug differ in their prior susceptibility to die), which could not be avoided by the inclusion of cumulative drug exposure exclusively as supposed by the authors.
Statins and aspirin are two medications frequently prescribed to individuals with diabetes, that have also been associated with decreased overall mortality in cancer patients. We assessed the independent effects of metformin, statins and aspirin after CRC diagnosis on overall mortality within GLDs users that started their treatment before cancer diagnosis (**Chapter 7**). The Cox regression model, with CRC diagnosis as baseline, included time-dependent variables of cumulative exposure to metformin, statins and aspirin after cancer diagnosis and time-dependent ever-never terms for drug exposure. Longer cumulative exposure to

metformin was not associated with overall mortality, while the favourable effect of statins increased with cumulative drug exposure. No statistically significant association between aspirin use and overall mortality was observed. Our findings support a drug effect of statins, independent of metformin and aspirin, in CRC patients using GLDs.

Most of the previous studies on the association between diabetes, cancer and mortality focussed on the effect of diabetes and its treatment on cancer, while the reverse effect of cancer and its treatment on diabetes controls has received very limited attention. In this thesis we aimed to evaluate the impact of cancer and its treatment on HbA_{1c}-values among individuals using GLDs for more than two years prior to their CRC diagnosis (**Chapter 8**). HbA_{1c}-values changed at the time of diagnosis of colon and rectal cancer, with levels decreasing from two years before cancer diagnosis till cancer diagnosis for both cancer types and increasing within the two years after cancer for colon cancer. The most profound HbA_{1c} changes were seen for patients with proximal colon tumours or those using anti-anaemic preparations before colon cancer diagnosis. These findings mean that the observed changes of HbA_{1c} in this study might just reflect the effects of anaemia and anti-anaemic preparations on HbA_{1c}, while the actual glucose metabolism does not change. Moreover, physicians should be aware of the possible presence of cancer among individuals that use GLDs and have a decrease in HbA_{1c}.
Since a diagnosis of cancer might impact medication adherence and good adherence to GLDs is crucial for achieving glycaemic control, in this thesis the impact of cancer on medication adherence among new users of GLDs was explored (**Chapter 9**). GLDs users who developed cancer during follow-up (cases) were matched with GLDs users without cancer during follow-up (controls). The Medication Possession Ratio (%; MPR) was used as indicator for medication adherence. While the difference in MPR between cases and controls changed significantly at the diagnosis of any type of cancer, the highest impact of cancer diagnosis on medication adherence was seen for patients with oesophageal, stomach, colon, pancreas and liver cancer and those with small-cell and non-small lung cancer, in which the difference in MPR at cancer diagnosis changed around 15%. In addition, more advanced cancer stages at diagnosis resulted in larger changes in MPR at the time of cancer diagnosis. The reason for the decline in MPR needs to be further elucidated among the different cancer types - is it the patient who prioritizes the fight against cancer or the advice of the physician to stop the treatment?

This thesis contributed to the evidence that the combined effect of cancer and diabetes results in a worse mortality than the sum of the individual effects of cancer

and diabetes. We revealed that higher mortality rates for EC patients with diabetes were most likely caused by diabetes as such. Thus, physicians should be encouraged to carefully treat these patients for their diabetes control to prevent the development of diabetes complications. Moreover, diabetes affects the proportion of CRC patients that received cancer treatment, which in turn might affect their chance of cure and thus the prognosis. Our and other studies increasingly suggest that there is no association between metformin and mortality among CRC patients, while the effects of statin use on mortality among cancer patients seems more promising. We showed that glycaemic control among individuals with diabetes improved and the adherence to GLDs decreased due to cancer. For the day-to-day clinical oncology and endocrinology practice the results of this thesis contribute to the awareness of the dangerous liaison between diabetes and cancer, with all his facets.

General discussion

As a result of the dramatic increase in the number of patients with cancer or diabetes[2-4], the number of newly diagnosed cancer patients who also have diabetes is expected to rise from about 5,500 per year in 2000 to 10,000 per year in 2015 in the Netherlands[2]. Therefore, it is of utmost importance to understand which factors contribute to the higher overall mortality seen among cancer patients with diabetes compared to those without diabetes[5-7].

The objective of this thesis was to understand how the combination of diabetes and cancer results in a worse mortality than the sum of the effects of the individual diseases. In this chapter, the main findings of the studies performed in this thesis will be discussed in a broader context. Several methodological issues are discussed that should be considered when interpreting the findings of the studies presented in this thesis. Future direction and implications of the research presented are discussed as well.

Main findings

Impact of diabetes on cancer treatment and outcomes

Many studies showed that endometrial cancer (EC) patients with pre-existing diabetes have a significant increased overall mortality compared to those without diabetes[5,7-11]. Whether this is the result of diabetes on EC-specific outcomes remains unknown. In this thesis, no association between diabetes status and recurrence rates was found. Furthermore, after adjusting for a higher FIGO stage at cancer diagnosis, no influence of diabetes on the EC-specific higher mortality was found. It has been suggested that a rapid tumour growth by insulin could explain the more advanced FIGO stages among diabetes patients[12], but an effect on recurrence rate should than be expected as well. After the publication of our

study, results of new studies were combined in a meta-analyses which showed no association between diabetes and EC-specific mortality either[13]. Since patients with EC have a good prognosis and the number of events for EC-specific outcomes is relatively low, this study question might require an even larger dataset than available for the published meta-analysis. Nevertheless, the higher mortality rates for EC patients with diabetes were most likely caused by diabetes as such. In summary, our study as well as others underline that physicians should be encouraged and motivated to carefully treat and follow EC patients with diabetes for their diabetes control to prevent the development of diabetes complications. Furthermore, postmenopausal women with diabetes might have a more advanced stage at EC diagnosis, resulting in a higher EC-specific mortality, so extra vigilance by the general practitioner for symptoms of EC is needed in this subgroup of patients.

Based on the results among CRC patients, it seems that CRC patients with diabetes are still treated less aggressively with regard to chemotherapy. CRC patients who do not receive optimal treatment for their cancer have less chance of cure and surviving this disease. However, we do not know whether the less aggressive treatment indicates that the clinicians appropriately responded to the potential higher risk of treatment complications or whether this was inappropriate. In contrast, the proportion of stage II/III rectal cancer patients with and without diabetes who received radiotherapy increased at a similar rate in recent years. In recent years, especially in patients with comorbidity, the overall well tolerated radiotherapy[15,16] is used as downstaging and not directly followed by surgery. This trend could partially explain the tremendous increase in radiotherapy in rectal cancer patients with diabetes.

Impact of drug exposure on mortality after cancer

The current literature regarding metformin as an anti-tumour agent is inconclusive[14-16]. We observed no protective effect of metformin on mortality among CRC patients, while others did. Direct comparison between our and other studies among CRC patients is difficult given the differences in study population and methodology that will be discussed later. However, one study that investigated the role of metformin on survival in breast cancer patients used a similar approach as we did and had comparable results[17]. This study failed to show a significant association between every additional year of cumulative exposure to metformin and overall and breast cancer-specific mortality[17]. In contrast, a recent study among prostate cancer patients showed that prostate cancer-specific mortality decreased by 24% for each additional 6 months of metformin use after the diagnosis of prostate cancer[1]. Is it biologically plausible that 6 months of metformin use reduces

mortality by 24%? Later in this general discussion I will explain how we came to the assumption that the hazard ratio in this study does not exclusively reflect the effect of metformin and might be subject to bias.
As many diabetes patients use a combination of metformin, statins and aspirin (in our cohort of GLDs users this proportion was 25%), it is justified to wonder if the suggested association between metformin use and overall mortality among cancer patients is explained by the concomitant use of aspirin or statins, and vice versa[18-20]. Within our analyses, the favourable effect of statins increased with cumulative drug exposure, supporting a drug effect of statins, independent of metformin and aspirin, in CRC patients using GLDs. Regarding the use of aspirin and statins, it should be noted that this study only investigated a subgroup, i.e. the individuals with diabetes. Thus, we have to be careful when comparing the results seen for statin users directly with other studies on statin use and overall mortality after cancer. Results from a study with a comparable methodology indicated that post-diagnostic use of statins was associated with a 24% decrease in prostate cancer mortality among newly diagnosed non-metastatic patients, with dose response relationships in terms of cumulative duration of use and cumulative dose[19]. This study had many strengths, since it circumvented many biases and one of the study outcomes was cancer-specific mortality[19].

Impact of cancer on glycaemic control and glucose lowering drug use

Most of the previous studies on the association between diabetes, cancer and mortality focussed on the effect of diabetes and its treatment on cancer, while the reverse effect of cancer and its treatment on diabetes control has received limited attention so far. In contrast to our hypothesis that the development of cancer and its treatment would increase the value of HbA_{1c}, the presence of cancer lowered HbA_{1c} with clear drops at the time of cancer diagnosis. According to a study on HbA_{1c} and survival, not only individuals with diabetes and recent HbA_{1c} values >9% (75 mmol/mol), but also those with recent HbA_{1c} values <6.5% (48 mmol/mol; OR 1.3; 95% CI 1.2-1.4) had higher mortality compared to those with recent 'normal' HbA_{1c} values between 6.5% and 9%[21]. The decrease of HbA_{1c} before the diagnosis of cancer might be the result of an abnormal metabolism due to the tumour, reduced food intake or weight loss, all associated with cancer cachexia[22-24]. Colon cancer patients who had a proximal colon tumour or used anti-anaemic preparations before cancer diagnosis had an even more profound decrease in HbA_{1c} pre-cancer diagnosis. In a study among 1,189 CRC patients, anaemia was prevalent in 30%, 40% and 68% of rectal, distal colon and proximal colon cancer, respectively[25]. Thus, patients with proximal colon tumours frequently use anti-anaemic preparations for their anaemia. Therefore, the rapid red cell turnover (i.e. great proportion of younger red cells) due to the treatment of anaemia might

result in falsely low HbA_{1c} levels in those with proximal colon tumours[26]. The observed changes of HbA_{1c} in this study might just reflect the effects of these factors on HbA_{1c}, while the actual glucose metabolism does not change. Consequently, physicians should be aware that the HbA_{1c} measure to monitor glycaemic control might be an inappropriate test in this subgroup of patients.
In this thesis a change in medication possession ratio (MPR) of 6% at the time of any cancer diagnosis was found. This difference translates to a difference of 2 days in a month that is not covered by the use of GLDs between patients with and without cancer. A 20% MPR difference between patients with and without cancer would be considered the cut-off for an adherent compared to a non-adherent GLDs user[27]. The difference in MPR at cancer diagnosis reached almost 20% among patients with gastro-intestinal cancers (colon, oesophagus, stomach, pancreas and liver cancer) and among patients with pulmonary cancers in which it was over 15%. Based on 20% to be considered non-adherent, would the observed differences of 6% and 15% be clinically significant? Interestingly, previous studies showed that relatively small changes in MPR are associated with changes in glycaemic control[28,29]. In one study, a statistically significant 48% decrease in the odds of poor glycaemic control (HbA_{1c} >8%; 64 mmol/mol) was found for each percentage increase in MPR (OR 0.52; 95% CI 0.44-0.62)[28]. Nevertheless, we previously showed that HbA_{1c} levels decreased at the time of cancer diagnosis, suggesting improved glycaemic control. Consequently, the physician might decide to discontinue GLDs because of improved glycaemic control, resulting in lower MPR ('worse' medication adherence) among individuals with diabetes. In conclusion, although we observed a lower medication adherence among GLDs users because of cancer the clinical implication has to be studied in more detail as many factors could have influenced this finding.

Methodological considerations

The investigation of the association between diabetes, GLDs, cancer and mortality is complex, and the studies in this thesis encounter some methodological strengths and weaknesses. The accurate analyses of diabetes status and drug exposure are important elements of studies in this research field, and are as important as other features of study design, adequate sample size and patient selection, appropriate adjustment for confounders, and the use of validated data sources[30]. In this chapter, the most important elements with regard to the methodological considerations of studies in this thesis are discussed.

Data source limitations

Eindhoven Cancer Registry

Patients included in the studies described in this thesis may have different cancer characteristics compared to other regions in the Netherlands. The region of the Eindhoven Cancer Registry (ECR) contains 10 community hospitals and no academic or specialized cancer hospitals, does not include one of the top three largest cities in the Netherlands and the population is somewhat older than the total Dutch population[31,32]. The ECR is worldwide unique in the registration of the presence of comorbid conditions at time of cancer diagnosis[33], which was essential for several of our studies.

However, while the ECR collects extensive data on the primary tumour and the initial treatment, it does not yet collect information on the presence of recurrent disease and the cause of death. The information on cause of death was additionally collected for our study among EC patients. This data collection was time-consuming, whereas defining the exact cause of death was difficult and subjective as confirmed by experts in the field[34]. Unreliable cause of death information may provide misleading results[35], which was illustrated by a previous study on CRC-specific survival, in which 34% of the rectal cancer patients were registered with colon cancer as the underlying cause of death[36]. Thus, although it is a strength of the study that we collected additional data regarding EC-specific survival, the found rate of EC-specific survival might be an over- or underestimation. The protective effect of statin use on overall mortality in this thesis might be highly attributed to the decrease in cardiovascular deaths instead of cancer deaths in this group of patients[37,38]. Since we could not investigate whether the lower over mortality among statin users was explained by the potential decrease in cardiovascular deaths, the lack of cause of death information is a major limitation. Another limitation is that this thesis missed important information on performance status of the patients, doses and dose adjustments of chemotherapy and treatment-related complications. The finding that CRC patients with diabetes less often received chemotherapy than those without diabetes might be an underestimation of the problem: Based on clinical experience it would be expected that many dose adjustments had taken place among cancer patients with diabetes that have not been registered and analysed in our studies[39].

PHARMO

A general problem using dispensing data to assess drug use is that we do not know if and when the dispensed drugs are actually ingested by patients[40]. Moreover, the out-patient pharmacy database does not include drugs used within the hospital or within nursing homes. This may have resulted in an overestimation of the effect of statins seen in this thesis, as patients who are sicker will be

hospitalised more often and thus have missing dispensing data more often.
The pharmacy database has information for drugs on prescriptions, while over the counter drugs, such as aspirins, could not be captured by our data. Thus, in this thesis only aspirin dispensings with the indication "platelet aggregation inhibition" (defined by their ATC code[41]) and considered low dose aspirin dispensings (≤100 mg daily) are included. Consequently, the misclassification of exposure due to over the counter low dose aspirin use is likely to be minimal, because low dose aspirin for this indication is only available on prescription in the Netherlands.

Combined ECR-PHARMO database
In this thesis the overall effects of drug exposure on mortality in a certain type of cancer could be investigated. However, subgroup analyses have been of limited value because of the relatively small sample size after careful selection of the study population. These subgroup analyses could be important to better understand the underlying mechanism for the association. Although the combined cohort now consists of 13 years of follow-up, after selecting patients that met all the criteria which were needed to give reliably results, the mean follow-up periods of about 2-3 years for overall mortality were relatively short. For the research questions within this thesis a longer duration and larger sample sizes are required to better assess the effect of cumulative exposure to metformin, statin and aspirin on mortality. In the near future, linkage of the Netherlands Cancer Registry with PHARMO will give more opportunities for new research with a cohort four times the current size.
Also, collaboration with international research groups in this field could improve our understanding of the association between diabetes, cancer and mortality. For example, the established network of the EASD Diabetes and Cancer Study Group (previously the Diabetes and Cancer Research Consortium (DCRC)) has a good infrastructure to combine data and to collaborate, especially when outcomes are rare[6,42]. This group, in which our research group participates, aims to develop and optimize methodological approaches required to address the complex relationships between diabetes, GLDs and cancer.

Bias and confounding
In 2005, a large observational study was published that reported a significant reduction in the cancer incidence with metformin use among 2,829 patients with type 2 diabetes[43]. This publication resulted in great interest in metformin as an anti-tumour agent and generated the hypothesis that metformin might lower cancer risk among patients with diabetes[43]. In the years after this study, many other studies showed similar effects of metformin on the risk of cancer[44,45]. In

addition, metformin seemed to have a protective effect on overall mortality among cancer patients as well[46,47]. But, today we understand that many of the earlier observational studies with too impressive hazard rates contained time-related biases and other limitations that artificially made metformin look like a 'wonderdrug' for the survival after cancer[6,16,30,48]. In this paragraph I will discuss the most important biases and discuss how was dealt with them in this thesis.

Allocation bias and cumulative drug exposure

Since the medication use of an individual with diabetes varies over time and the effect of exposure will depend on duration of use, dose and adherence to therapy, a dichotomized variable for drug use frequently used in previous studies[39,42-45] will not be sufficient[49]. Moreover, the use versus the non-use of a drug is based on the decision of a physician, who might even base his decision on the prognosis of the patient. This type of bias in pharmaco-epidemiology, known as allocation bias (those prescribed the drug of interest may differ in their prior susceptibility to survive after cancer when compared to those not prescribed the drug), has received increasing attention in the field of diabetes and cancer. It is now advised to analyse cumulative exposure in order to prevent this bias[30,48]. The cumulative drug exposure represents the daily or monthly drug use and is not influenced by the differences between users and non-users of the drug of interest[30,48]. The inclusion of this cumulative exposure in our studies strengthens the results while the hazard ratio for the cumulative exposure to the specific drug gives the effect of this drug on survival for every additional day or month of use.

Incident versus prevalent users

To calculate the cumulative exposure of a specific type of drug, the exact duration of drug use needs to be known. Since this duration is known for incident users (i.e. new users; started with GLDs after entrance in the ECR-PHARMO cohort) and not for prevalent users (i.e. started with GLDs at any time before entrance in the ECR-PHARMO cohort), prevalent users would ideally be excluded[50]. Due to the sample sizes we were not always able to exclude the prevalent users for all studies described in this thesis. Nevertheless, sensitivity analyses excluding prevalent users were always performed. Moreover, CRC patients without metformin use before cancer might differ from those who did use metformin before cancer. These patients might differ in their diabetes severity, cancer stage at diagnosis and administration of cancer treatment and thus have a different prognosis already at cancer diagnosis. Also, CRC patients who started with GLDs after cancer diagnosis might start as a result of the well-known prednisone induced hyperglycaemia during cancer treatment[51]. In our study investigating the effects of metformin, statins and aspirin, we were able to adjust for many confounding factors, but not

for the presence of diabetes complications, BMI, cholesterol levels and other laboratory results. Therefore, residual confounding most likely remained.

Immortal time bias

The most important type of bias that has been criticized regarding previous studies on metformin and mortality after cancer is immortal time bias[48]. If the exposure time between cancer diagnosis and the first dispensing of metformin is classified as exposed time, than this time is 'immortal', since the patient must be alive to receive the first metformin dispensing[48]. This bias is known to overestimate the effect of a drug: the drug seems to be protective while it might have no 'real' effect[48,52]. To overcome this bias the exposure variables in Cox proportional hazards models need to be time-dependent, which was done in the studies presented in this thesis[48]. In these analyses the person-time is classified as unexposed until the first metformin dispensing and the remaining time (after the first dispensing) is classified as exposed to metformin[48].

Often in studies that investigate effects of drug exposure, cumulative exposure represents users with different drug exposures, but also non-users with a cumulative exposure equal to zero. In that situation, the events for overall mortality for non-users will all be clustered at the cumulative exposure of zero months. As a result this point probably represents the majority of events and is therefore particularly important in the calculation of the hazard ratio for cumulative exposure. As a consequence, the most important comparison of events is the one between zero months and for example 6 months of cumulative exposure. The hazard ratio of cumulative exposure for the first 6 months of use influences to a large extent the slope of the hazard for every following 6 months. Thus, in this study setting, the hazard ratio of cumulative exposure is strongly influenced by the prior susceptibility to die for non-users compared to users, as previously described, known as allocation bias. With the inclusion of time-dependent ever-never terms for the studied drugs in the model, the hazard ratio of the cumulative effect term seems to be not dependent on the events in the unexposed group[53]. However, the inclusion of time-dependent ever-never terms is still subject of recent debate. Some experts in the field fear that the inclusion of both cumulative exposure and ever-never terms in a model introduces collinearity (i.e. two variables are highly correlated), since never users always have a cumulative exposure of zero days, while ever users have cumulative exposures of at least one day. Epidemiologist currently debate about this problem and for now it is advised for new studies to show different kind of models[54-56]. Although in the studies in this thesis not all models were shown, for our study in chapter 7 this recent discussion has stimulated us to additionally conduct the analyses without ever-never terms. It appeared then

that the use of statin was even more protective.

Dose of exposure of a drug of interest

One further methodological consideration is the association between dose and duration of exposure – to how many milligrams of the drug was the patient exposed during the time studied[30]? The construction of a combined measure can be carried out for the product of dose and duration. The corresponding analyses are even more complex than the analyses with time-dependent cumulative exposure. But, these analyses might show a dose-response relationship for metformin, statins or aspirin use, thus the absence of them was a weakness of our pharmaco-epidemiological studies. However, peaks of intense exposure to the drug might have a greater impact on the outcome than the average exposure, and a simple dose-duration product cannot show substantial variations in exposure with time[30]. Current epidemiological studies investigate doses safely obtained in the clinical setting, while it has become clear that many preclinical studies use concentrations of metformin considerably higher than those[57,58]. The doses of metformin currently used in many oncology trials are those shown to be effective for glucose control. If metformin has an effect on mortality, then there is a need to establish the appropriate dose of metformin for its proposed anti-cancer effects[58].

Sick-stopper bias

Sick-stopper bias is the result of the fact that sicker patients with a poorer prognosis might be more likely to discontinue preventative treatments for non-symptomatic illness. This type of bias may be important for different types of medications used by patients under study in this thesis. For example, among individuals with diabetes, the use of statin as secondary prevention is advised to certain patient groups with low-density lipoprotein (LDL) >2,5 mmol/l and ≥10% chance of cardiovascular disease or mortality in 10 years based on a risk assessment[59,60]. Because statins are prescribed to prevent and not to treat cardiovascular disease, the non-adherence to statins is reasonably high[61,62]. Thus, especially the effect of statin use on survival might be confounded by sick stopper bias, because sicker patients with a poorer prognosis might be more likely to discontinue preventative treatments for non-symptomatic illness[63]. In our study after adjusting for the medication adherence and after dealing with the discontinuation of statin treatment just before death (by changing unexposed time after discontinuation into exposed time), this study still revealed a protective effect of statins on overall mortality among CRC patients. Since we were not able to verify which patients indeed discontinued their statin treatment, these analyses are suboptimal.

Healthy user bias

Another bias typical of research on effects of statins is healthy user bias, as statin users have been previously described as a selection of individuals who are more health-conscious than those who do not use this drug (while needing it)[63,64]. This could have influenced our results and might have overestimated the protective effect of statins on overall mortality, since individuals that are more health-conscious are also likely to pay more attention to other prognostic lifestyle factors[64]. But in contrast to this hypothesis, in our cohort and other studies statin users seemed to be less healthy than non-statin users, with higher numbers of co-medication, indicating a higher prevalence of comorbidities[19].

Unfortunately there is no consensus on the optimal approach to avoid sick stopper bias and healthy user bias[63,65,66], thus the potential presence of both remains an important limitation of the studies in this thesis and might have overestimated the protective effect of statins.

Results from a study with comparable methodology as in chapter 7 indicated that the post-diagnostic use of statins was associated with a 24% decrease in prostate cancer mortality among newly diagnosed non-metastatic patients[19]. This study had many strengths, it circumvented many biases and included a latency period of 1 year, to take into account a biologically meaningful latency time window given that short duration exposures are unlikely to be associated with the mortality outcomes[19,67]. In our analyses in chapter 5 and 7 we were not able to include this latency period because our follow-up time was rather short which is a weakness of our studies. Nonetheless, it remains questionable what the right duration of this period is among cancer patients.

Residual confounding

The review in this thesis underlined that the association between diabetes and prognosis in cancer patients is extremely complex, since many underlying risk factors, such as age, lifestyle factors, smoking status, comorbidities and/or metabolic factors play a role in this association[68,69]. In this thesis using the ECR-PHARMO cohort information about many important factors was available. However, as we only had access to clinical data for a small proportion of our patients, we were not able to include information on cholesterol level, HbA_{1c} and BMI in all our analyses. The influence of these metabolic factors on overall mortality in GLDs users might be of interest and should be evaluated in future studies. Moreover, the HbA_{1c} goal attainment might be more important for the prognosis of a patient than the dose and duration of exposure to metformin or sulfonylurea derivatives in which we are interested. Likewise, the protective effect of statins observed in this thesis could be the result of improvements in cholesterol levels

and in that way indirectly influence the cardiovascular mortality[59,60].
Because of the high proportion of comorbid diseases, diabetes guidelines advice an abundance of co-medication for individuals that already use GLDs[70]. Statins and aspirin are two of these co-medications frequently prescribed to individuals with diabetes, i.e. around 50% of them use statins and 40% use aspirin according to the current international literature[71-74]. In the study described in chapter 7 of this thesis, 25% of the CRC patients used a combination of metformin, statins and aspirin. Interestingly, metformin, statin and aspirin users, also used significantly more of the frequently prescribed beta blocking agents and renin-angiotensin system agents compared to those not using the studied drugs. Although we included a sensitivity analyses that adjusted for the cumulative exposures to these other co-medications that still showed protective results for statins, it is questionable whether this abundance of cumulative exposures in the model in combination with the small sample size might have flawed the model[75]. Ideally, new studies should take into account all the different co-medications prescribed to the diabetes population, when studying one of them[19].

Matching
In this thesis, in two studies it appeared best to match cases and controls within the ECR and ECR-PHARMO cohort to efficiently answer the research question. 'Matching' is defined as any method that aims to balance the distribution of covariates in the group of cases and controls[76,77]. In our study in chapter 3 the outcome values were not yet available and matching was preferred to select subjects for additional data collection, since it was not possible to collect the data for all 1,644 EC patients. Although matching was highly efficient, as a result of the matching on age our findings are less comparable with previous studies, because in our study older EC patients without diabetes were overrepresented.
In chapter 8 we applied a matching approach to reduce bias and confounding in estimating the impact of cancer on medication adherence. Users of GLDs with a primary diagnosis of any cancer were considered cases and those without a diagnosis of cancer were eligible as controls. Cases and controls were matched - with replacement and a maximum of 4 controls per case – on five different criteria which needed to be the same for cases and their controls. A strength of that approach was that we were able to match on five important variables which improved statistical efficiency. Nonetheless, by matching on these 5 variables, the potential effect of any of these 5 factors can no longer be studied directly[76]. Thus, with this approach we were not able to show if the impact of cancer is for example different for patients that used metformin compared with sulfonylurea derivatives, because we matched patients on the type of GLDs they used. The optimal ratio in which to sample cases and controls is still subject of discussion[77]. When controls

are easier to obtain as in our study with retrospective data it is more common to sample more controls than cases. At first we sampled as much controls as possible, which resulted in an imbalance, because of the matching criteria some controls and cases were overrepresented. The maximum for controls was set on four, more than four controls did not increase our power, while the analyses with less than four controls resulted in less clear point estimates, such an influence of number of controls was already demonstrated a long time ago[77].

Medication adherence

Since medication adherence, measured every month as the medication possession ratio (MPR)[78], is a continuous variable, ranging from 0% - 100%, linear regression was performed to test statistically the impact of cancer. The interrupted time series analysis is only valid to the extent that the cancer diagnosis was the only event that changed over time and the only that was able to change the monthly calculated MPR[79]. In our study, described in chapter 9, the visit of an endocrinologist by the patient because of vague complaints of an undiagnosed cancer might be a competing event, since medication adherence might be affected by this visit[80]. Moreover, missing dispensing data – for example because of hospitalisations for cancer– might falsely give the impression that medication adherence had fallen when in fact the data was simply missing. Thus, due to the presence of competing events and the missing dispensing data because of hospitalisations for cancer, the impact of cancer on adherence to GLDs might have been overestimated in chapter 9.

The impact of different types of cancer

The first studies that evaluated the impact of diabetes on cancer often grouped all cancer patients in their analyses. Nowadays the importance of evaluating the reciprocal impact of diabetes and different types of cancer on mortality is acknowledged. Findings of this thesis demonstrate that even between different types of colon cancers the effect can be different, colon cancer patients with diabetes had more often a tumour located in the proximal colon compared to those without diabetes. Furthermore, the presence of prostate and breast cancer seemed to have no influence on medication adherence in GLDs users, while among gastrointestinal cancers and pulmonary cancer the impact of cancer was large. Whereas a strength of our study was that we was able to study the cancer types separately, for the future it is of great value to even study different subgroups within a cancer type. Consequently, large cohorts, both national and international, are required.

Implications of the study findings and future direction

The results presented in this thesis have several implications for clinical practice and future research. Recommendations for future research are based on questions that remain after or are evoked by studies in this thesis. Some of the future research questions can be answered with the expansion of the ECR-PHARMO cohort or with the linkage of this cohort with new datasets, as will be discussed below.

Implications for practice

- Results of the studies in this thesis indicate that there exists a dangerous liaison between diabetes and cancer. The prevalence of diabetes among many types of cancer appears to be higher than in an age-matched group without cancer. Also, physicians should be aware that patients with both diseases have higher overall mortality and might have a higher stage at cancer diagnosis, while they should criticize their own choices since these patients are treated less aggressively for their cancer.
- From the diabetes point of view, this thesis showed no evidence for changes in practice among those who also were diagnosed with cancer in terms of GLDs or the co-medications statins and aspirin to control for macrovascular complications of diabetes.
- Glycaemic control improved around the time of cancer diagnosis and adherence to GLDs decreased due to cancer among individuals with diabetes. A physician might decide to discontinue GLDs because of the improved glycaemic control, resulting in 'worse' medication adherence among individuals with diabetes. However, physicians should be aware that measuring HbA_{1c} to monitor glycaemic control might be an inappropriate test in patients with diabetes and (un)diagnosed cancer because the use of anti-anaemic preparations seems to falsely lower HbA_{1c}.

Implications for research

- This thesis suggests that between the different groups of GLDs users major differences in prognosis exist that are not related to the drug use itself, but rather to patient characteristics. There is a need for studies that investigate the difference in co-medication, hospitalisations, laboratory results and lifestyle between metformin and sulfonylurea derivatives users and between patients with and without diabetes to understand the impact of these on the observed mortality differences.
- To study the effects of drug use and diabetes status on mortality among cancer patients in more detail, the effects on cancer-specific outcomes and quality of life might be more important than those on overall mortality. New studies should invest in additional data collection to give more insight into the role

of metformin and co-medications in the diabetes population on patient reported and disease-specific outcomes, such as cancer-specific mortality and recurrence risk.

- With the studies in this thesis the evidence is now mounting against an association between metformin, CRC and mortality. A careful reassessment of the previous observational studies and the methods used in these studies is now warranted before more randomised controlled trials of metformin as a treatment for cancer are initiated.
- Although this thesis showed promising results for statin use, additional well-conducted observational studies with large sample sizes are needed that optimal deal with sick stopper bias to confirm our findings. After this, the launch of expensive randomized controlled trials assessing the effect of statins in the adjuvant setting will be justified and of great value to change practice.
- As hypothesised, this thesis showed that cancer impacts the use of GLDs and glycaemic control among individuals with diabetes. These findings substantiate the relevance for further research that assesses the influence of cancer on diabetes aspects, such as glucose control and diabetes complications, and indirectly survival.

Future research

Datasets and future studies

The expansion of the ECR-PHARMO cohort in the near future is of utmost importance for the implications for research as mentioned above and for studying less frequent cancer types and drug types. Besides that the cohort will expand every annual update, resulting in longer follow-up of existing cancer patients, the PHARMO Institute will further stimulate pharmacists, general practitioners and others to share their data. More interestingly is the upcoming linkage of the Netherlands Cancer Registry (managed by the Netherlands Comprehensive Cancer Organisation (IKNL)) with PHARMO, which will result in an overlapping area in the Netherlands of an estimated 4 million inhabitants. This expansion gives opportunities for future research, since a key limitation of the studies in this thesis is the small cohort size in certain subgroups studied. With the geographical increase the possibilities to focus on clinical laboratory values are immense, for example, among statin users, we might be able to see if the improvements in cholesterol levels due to statins explain the protective effects on overall mortality. In addition, with this data we could explore patterns of Hb and BMI around the diagnosis of cancer, to see if they follow a similar pattern as HbA_{1c}.

In addition to the increase in cohort size, new linkages with other databases will increase the value of the established ECR-PHARMO link. For this thesis the out-patient pharmacy database and the clinical laboratory database from PHARMO

was used, while these databases can be additionally linked with a general practitioner (GP) database and the database of the Dutch Medical Registry (LMR)[81]. The GP database captures additional information on physician-linked indications for therapy, comorbidity, lifestyle factors (such as smoking status), drug prescriptions, laboratory values, and referrals to specialists. With this database, researchers are able to investigate whether smoking is an effect modifier in the association between diabetes and cancer outcomes. The records of the Dutch Medical Registry include detailed information about admission and discharge dates, primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, consultations with medical specialists and the length of stay. With these extra databases one would be able to provide an comprehensive overview of the differences between subgroups of diabetes patients, such as the differences between metformin and sulfonylurea derivatives users and between cancer patients with and without diabetes.

The association between diabetes, GLDs and cancer-specific outcomes is important in the overall association between diabetes and mortality in CRC patients. The metastatic spread of CRC might give further clues, since a recent study with ECR data and information on CRC recurrence observed different patterns of metastatic spread between colon and rectal cancer patients[82]. In the future we will be able to link this dataset with the PHARMO Database Network to investigate differences in risk of recurrence as well as patterns of metastatic spread between patients with and without diabetes and those using specific types of drugs. In addition, these risks and patterns could be studied in relation to cancer-specific mortality, as cause of death information can be obtained from Statistics Netherlands (CBS)[83].

Health-related quality of life

The impact of diabetes and GLDs among cancer patients should also be studied with regard to patient-reported outcomes such as health-related quality of life (HRQoL). Recently, in cancer research, more attention is being paid to HRQoL of cancer survivors, where previously the focus was more on objective outcome measures such as mortality[84]. Previous research reported that both cancer and diabetes individually affect HRQoL. However, it remains unclear to what extent the combination of cancer and diabetes has an independent negative effect on HRQoL.

Previous studies that investigated this, used the PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) registry, which is linked with the ECR[85]. Within the PROFILES registry cancer survivors are selected from the ECR and via questionnaires patient-reported outcome data are available[85]. A previous study with these data assessed the difference in explained variance of HRQoL between comorbidity, sociodemographic

characteristics and cancer characteristics among patients with thyroid cancer, CRC and (non-)Hodgkin lymphoma[84]. This study showed that in comparison with sociodemographic and cancer characteristics, comorbidity explained more variance in physical function, emotional function, pain, and fatigue. Another study using the PROFILES data assessed the impact of having both CRC and the comorbidity, diabetes, on HRQoL and sexual functioning[86]. Having both CRC and diabetes did not result in lower HRQoL and sexual functioning than the sum of the individual effects of both diseases[86]. However, when including only CRC patients, CRC patients with diabetes reported lower physical functioning and more male sexual problems than CRC patients without diabetes[86].
The two studies provide an insight into the effect of cancer and comorbidities, especially diabetes, on problems with HRQoL and sexual functioning[84,86]. Although these patient-reported outcomes are becoming more important, more research is needed to prove their relevance in evaluation of treatments[86]. In addition, to study the effects of specific GLDs on quality of life among cancer patients, the PROFILES registry together with the expansion of the ECR-PHARMO cohort would be perfect[85].

Concluding remarks

The higher mortality among cancer patients with diabetes compared to those without diabetes is worrying as the number of individuals diagnosed with both diseases is expected to increase even more. In this thesis, I described that among EC patients the higher mortality rates for EC patients with diabetes were most likely caused by diabetes as such. Physicians should thus be encouraged to carefully treat these patients for their diabetes control to prevent the development of diabetes complications. Moreover, having diabetes affects the chance of receiving certain cancer treatment, which in turn affects the prognosis. From the diabetes point of view, there is no call for changes in clinical practice in terms of metformin, while more research on the effect of statin use on overall mortality in cancer patients is needed. Journal editors and reviewers in the diabetes and cancer fields must be aware of methodological pitfalls and support the pursuit of unbiased interpretations. In this thesis, I revealed that the diagnosis of cancer does impact diabetes and its treatment, thus the lack of interest from the field regarding this is unfortunate and in the future this should be overtaken. For the day-to-day clinical oncology and endocrinology practice the results of my thesis increase the evidence that physicians should be aware of the dangerous liaison between diabetes and cancer, with all its facets.

References

1. Margel D, Urbach DR, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Metformin Use and All-Cause and Prostate Cancer-Specific Mortality Among Men With Diabetes. J Clin Oncol. 2013;31(25):3069-75.
2. Cancer in the Netherlands till 2020 (2011) Trends and prognoses. Signalling Committee Cancer of the Dutch Cancer Society, Amsterdam. ISBN 90-71229-00-8.
3. Imes CC, Burke LE. The Obesity Epidemic: The United States as a Cautionary Tale for the Rest of the World. Curr Epidemiol Rep. 2014;1(2):82-8.
4. Baan CA, van Baal PH, Jacobs-van der Bruggen MA, Verkley H, Poos MJ, Hoogenveen RT, et al. [Diabetes mellitus in the Netherlands: estimate of the current disease burden and prognosis for 2025]. Ned Tijdschr Geneeskd. 2009;153(22):1052-8.
5. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754-64.
6. Renehan AG, Yeh HC, Johnson JA, Wild SH, Gale EA, Moller H. Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. Diabetologia. 2012;55(6):1619-32.
7. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer. 2007;120(9):1986-92.
8. Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. Int J Gynecol Cancer. 2007;17(2):441-6.
9. Folsom AR, Anderson KE, Sweeney C, Jacobs DR, Jr. Diabetes as a risk factor for death following endometrial cancer. Gynecol Oncol. 2004;94(3):740-5.
10. Steiner E, Eicher O, Sagemuller J, Schmidt M, Pilch H, Tanner B, et al. Multivariate independent prognostic factors in endometrial carcinoma: a clinicopathologic study in 181 patients: 10 years experience at the Department of Obstetrics and Gynecology of the Mainz University. Int J Gynecol Cancer. 2003;13(2):197-203.
11. Boll D, Verhoeven RH, van der Aa MA, Lybeert ML, Coebergh JW, Janssen-Heijnen ML. Adherence to national guidelines for treatment and outcome of endometrial cancer stage I in relation to co-morbidity in southern Netherlands 1995-2008. Eur J Cancer. 2011;47(10):1504-10.
12. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009;16(4):1103-23.
13. Liao C, Zhang D, Mungo C, Andrew Tompkins D, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol. 2014.
14. Lega IC, Shah PS, Margel D, Beyene J, Rochon PA, Lipscombe LL. The effect of metformin on mortality following cancer among patients with diabetes. Cancer Epidemiol Biomarkers Prev. 2014.
15. Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, DeCensi A, et al. Metformin and Cancer Risk and Mortality: A Systematic Review and Meta-analysis Taking into Account Biases and Confounders. Cancer Prev Res (Phila). 2014.
16. Suissa S, Azoulay L. Metformin and cancer: mounting evidence against an association. Diabetes Care. 2014;37(7):1786-8.
17. Lega IC, Austin PC, Gruneir A, Goodwin PJ, Rochon PA, Lipscombe LL. Association between metformin therapy and mortality after breast cancer: a population-based study. Diabetes Care. 2013;36(10):3018-26.
18. Tural D, Yuce D, Kilickap S. Mortality in Prostate Cancer and Use of Statins. J Clin Oncol. 2014.
19. Yu O, Eberg M, Benayoun S, Aprikian A, Batist G, Suissa S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol. 2014;32(1):5-11.
20. Wu JW, Boudreau DM, Park Y, Simonds NI, Freedman AN. Commonly used diabetes and cardiovascular medications and cancer recurrence and cancer-specific mortality: a review of the literature. Expert Opin Drug Saf. 2014;13(8):1071-99.
21. Nicholas J, Charlton J, Dregan A, Gulliford MC. Recent HbA1c values and mortality risk in type 2 diabetes. population-based case-control study. PLoS One. 2013;8(7):e68008.
22. Kaelin WG, Jr., Thompson CB. Q&A: Cancer: clues from cell metabolism. Nature. 2010;465(7298):562-4.

23. Fearon KC, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab. 2012;16(2):153-66.

24. Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D. Long-term effects of modest weight loss in type II diabetic patients. Arch Intern Med. 1987;147(10):1749-53.

25. Edna TH, Karlsen V, Jullumstro E, Lydersen S. Prevalence of anaemia at diagnosis of colorectal cancer: assessment of associated risk factors. Hepatogastroenterology. 2012;59(115):713-6.

26. Gallagher EJ, Le Roith D, Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. J Diabetes. 2009;1(1):9-17.

27. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. Curr Med Res Opin. 2009;25(9):2303-10.

28. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal effects of medication nonadherence on glycemic control. Ann Pharmacother. 2014;48(5):562-70.

29. Lawrence DB, Ragucci KR, Long LB, Parris BS, Helfer LA. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. J Manag Care Pharm. 2006;12(6):466-71.

30. Walker JJ, Johnson JA, Wild SH. Diabetes treatments and cancer risk: the importance of considering aspects of drug exposure. Lancet Diabetes Endocrinol. 2013;1(2):132-9.

31. Siesling S, van der Aa MA, Coebergh JW, Pukkala E, Working Group of The Netherlands Cancer R. Time-space trends in cancer incidence in the Netherlands in 1989-2003. Int J Cancer. 2008;122(9):2106-14.

32. Statistics Netherlands; http://statline.cbs.nl.

33. van Leersum NJ, Janssen-Heijnen ML, Wouters MW, Rutten HJ, Coebergh JW, Tollenaar RA, et al. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010. Int J Cancer. 2013;132(9):2157-63.

34. Flanders WD. Inaccuracies of death certificate information. Epidemiology. 1992;3(1):3-5.Hinchliffe SR, Abrams KR, Lambert PC. The impact of under and over-recording of cancer on death certificates in a competing risks analysis: a simulation study. Cancer Epidemiol. 2013;37(1):11-9.

35. van de Poll-Franse LV, Haak HR, Coebergh JW, Janssen-Heijnen ML, Lemmens VE. Disease-specific mortality among stage I-III colorectal cancer patients with diabetes: a large population-based analysis. Diabetologia. 2012;55(8):2163-72.

36. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339(19):1349-57.

37. Lipworth L, Fazio S, Kabagambe EK, Munro HM, Nwazue VC, Tarone RE, et al. A prospective study of statin use and mortality among 67,385 blacks and whites in the Southeastern United States. Clin Epidemiol. 2014;6:15-25.

38. van Gils CW, Koopman M, Mol L, Redekop WK, Uyl-de Groot CA, Punt CJ. Adjuvant chemotherapy in stage III colon cancer: guideline implementation, patterns of use and outcomes in daily practice in The Netherlands. Acta Oncol. 2012;51(1):57-64.

39. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005;58(4):323-37.

40. World Health Organization. Collaborating Centre for Drug Statistics Methodology - ATC/DDD index. Accessed at www.whocc.no/atc_ddd_index, 2014.

41. http://www.easd.org//images/easdwebfiles/EASD_CANCER/index.html.

42. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. Bmj. 2005;330(7503):1304-5.

43. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2010;3(11):1451-61.

44. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One. 2012;7(3):e33411.

45. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care. 2006;29(2):254-8.

46. Currie CJ, Poole CD, Jenkins-Jones S, Gale EA, Johnson JA, Morgan CL. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care. 2012;35(2):299-304.

47. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care. 2012;35(12):2665-73.

48. Stricker BH, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. Eur J Epidemiol. 2010;25(4):245-51.

49. Danaei G, Tavakkoli M, Hernan MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. Am J Epidemiol. 2012;175(4):250-62.

50. Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15(5):469-74.

51. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008;167 (4):492-9.

52. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012;55(11):2929-37.

53. http://bendixcarstensen.com/DMCa/Zanders/Zanders-JCO-comm.pdf.

54. Penney KL, Stampfer MJ. Reply to M.M.J. Zanders et al. J Clin Oncol. 2014;32(7):702-3.

55. Margel D, Urbach D, Fleshner N, Austin PC. Reply to M.M.J. Zanders et al. J Clin Oncol. 2014;32(7):702.

56. Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. Cancer Discov. 2012;2(9):778-90.

57. Badrick E, Renehan AG. Diabetes and cancer: 5years into the recent controversy. Eur J Cancer. 2014;50(12):2119-25.

58. Bouma M, Rutten GE, de Grauw WJ, Wiersma T, Goudswaard AN. [Summary of the practice guideline 'Diabetes mellitus type 2' (second revision) from the Dutch College of General Practitioners]. Ned Tijdschr Geneeskd. 2006;150(41):2251-6.

59. Kroon AA. [Dutch guideline for cardiovascular risk management: a consensus model]. Ned Tijdschr Geneeskd. 2012;156(36):A5196.

60. Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. Value Health. 2000;3(6): 417-26.

61. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother. 2010;44(9):1410-21.

62. Stavrou EP, Buckley N, Olivier J, Pearson SA. Discontinuation of statin therapy in older people: does a cancer diagnosis make a difference? An observational cohort study using data linkage. BMJ Open. 2012;2(3).

63. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol. 2007;166(3):348-54.

64. Wang SV, Gagne JJ, Glynn RJ, Schneeweiss S. Case-crossover studies of therapeutics: design approaches to addressing time-varying prognosis in elderly populations. Epidemiology. 2013;24(3):375-8.

65. Glynn RJ, Knight EL, Levin R, Avorn J. Paradoxical relations of drug treatment with mortality in older persons. Epidemiology. 2001;12(6):682-9.

66. Chubak J, Boudreau DM, Wirtz HS, McKnight B, Weiss NS. Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. J Natl Cancer Inst. 2013;105(19):1456-62.

67. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin. 2010;60(4):207-21.

68. Sullivan PW, Morrato EH, Ghushchyan V, Wyatt HR, Hill JO. Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000-2002. Diabetes Care. 2005;28(7):1599-603.

69. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80.

70. van Dijk L, Wolters I, de Bakker DH. NIVEL: Farmaceutische zorg in de integrale bekostiging, http://www.nivel.nl/sites/default/files/bestanden/Rapport-Farmaceutische-zorg-in-tegrale-bekostiging.pdf. 2011.

71. Ekstrom N, Cederholm J, Zethelius B, Eliasson B, Fharm E, Rolandsson O, et al. Aspirin treatment and risk of first incident cardiovascular diseases in patients with type 2 diabetes: an observational study from the Swedish National Diabetes Register. BMJ Open. 2013;3(4).

72. Smiechowski B, Azoulay L, Yin H, Pollak MN, Suissa S. The use of metformin and colorectal cancer incidence in patients with type II diabetes mellitus. Cancer Epidemiol Biomarkers Prev. 2013;22(10):1877-83.

73. Wienbergen H, Senges J, Gitt AK. Should we prescribe statin and aspirin for every diabetic patient? Is it time for a polypill? Diabetes Care. 2008;31 Suppl 2:S222-5.

74. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2007;165(6):710-8.

75. Rose S, Laan MJ. Why match? Investigating matched case-control study designs with causal effect estimation. Int J Biostat. 2009;5(1): Article 1.

76. Breslow N. Design and analysis of case-control studies. Annu Rev Public Health. 1982;3:29-54.

77. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. Med Care. 2008;46(11):1125-33.

78. Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. Acad Pediatr. 2013;13(6 Suppl):S38-44.

79. Curkendall SM, Thomas N, Bell KF, Juneau PL, Weiss AJ. Predictors of medication adherence in patients with type 2 diabetes mellitus. Curr Med Res Opin. 2013;29(10):1275-86.

80. www.dutchhospitaldata.nl.

81. van Gestel YR, de Hingh IH, van Herk-Sukel MP, van Erning FN, Beerepoot LV, Wijsman JH, et al. Patterns of metachronous metastases after curative treatment of colorectal cancer. Cancer Epidemiol. 2014.

82. van Erning FN, van Steenbergen LN, Lemmens VE, Rutten HJ, Martijn H, van Spronsen DJ, et al. Conditional survival for long-term colorectal cancer survivors in the Netherlands: who do best? Eur J Cancer. 2014;50(10):1731-9.

83. Vissers PA, Thong MS, Pouwer F, Zanders MM, Coebergh JW, van de Poll-Franse LV. The impact of comorbidity on Health-Related Quality of Life among cancer survivors: analyses of data from the PROFILES registry. J Cancer Surviv. 2013;7(4):602-13.

84. van de Poll-Franse LV, Horevoorts N, van Eenbergen M, Denollet J, Roukema JA, Aaronson NK, et al. The Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship registry: scope, rationale and design of an infrastructure for the study of physical and psychosocial outcomes in cancer survivorship cohorts. Eur J Cancer. 2011;47(14):2188-94.

85. Vissers PA, Thong MS, Pouwer F, den Oudsten BL, Nieuwenhuijzen GA, van de Poll-Franse LV. The individual and combined effect of colorectal cancer and diabetes on health-related quality of life and sexual functioning: results from the PROFILES registry. Support Care Cancer. 2014.

Nederlandse samenvatting (Dutch summary)

Inleiding

Kanker en diabetes (in de volksmond ook wel 'suikerziekte' genoemd) zijn twee veel voorkomende ziekten die wereldwijd de gezondheid van veel mensen beïnvloedt. Van zowel diabetes als kanker is nog niet geheel bekend hoe de ziekte ontstaat en waardoor deze wordt veroorzaakt. Diabetes en kanker zijn elk het onderwerp van vele studies wereldwijd.

Kanker

Kanker, ook wel een kwaadaardige tumor genoemd, wordt ingedeeld op basis van de plaats in het lichaam waar de kanker ontstaat. Zo noemen we kanker die uitgaat van de dikkedarm, dikkedarmkanker. In 2013, kregen mannen in Nederland het vaakst: prostaat- (21%), huid- (14%) en dikkedarmkanker (14%). Vrouwen kregen het vaakst borst- (30%), huid- (14%) en dikkedarmkanker (12%). In dit proefschrift heb ik mij vooral op dikkedarmkanker gericht, omdat dit type kanker veel voorkomt en wordt gezien bij zowel mannen als vrouwen.
Kanker kan zich verspreiden naar verschillende delen van het lichaam via het bloed of het lymfestelsel. Het stadium van de kanker is een maat voor de verspreiding van de kanker en de grootte van de tumor. Kanker wordt meestal behandeld met chirurgie, radiotherapie (bestraling) en/of chemotherapie.

Diabetes

Bij volwassenen met diabetes is type 2 diabetes veruit de meest voorkomende soort diabetes. Mensen met diabetes hebben hoge glucosespiegels in het bloed. Bij gezonde mensen zorgt insuline - gemaakt in de alvleesklier - ervoor dat het te veel aan glucose in het bloed wordt opgenomen in de lever en spieren. Maar bij mensen met type 2 diabetes werkt insuline niet goed en is er ook een tekort aan insuline. Hierdoor blijven de glucosespiegels in het bloed hoog.
De meeste patiënten met diabetes hebben bij de vaststelling van de ziekte (de diagnose) geen klachten. Bij een bloedonderzoek wordt toevallig een verhoogde glucosewaarde gevonden. De meest voorkomende klachten die mensen met diabetes bij hun diagnose hebben zijn: veel plassen, dorst, wazig zien en soms gewichtsverlies. De diagnose diabetes wordt meestal gesteld op basis van een nuchtere bloedglucose die hoger is dan 7,0 mmol/L. Nadat diabetes is vastgesteld bij een persoon, wordt de bloedglucose elke 3 tot 6 maanden gecontroleerd door het meten van de Hemoglobine A_{1c} (HbA_{1c})-waarde in het bloed. Deze waarde geeft aan hoeveel glucose zich in het bloed gehecht heeft aan hemoglobine, het zuurstoftransporteiwit in de rode bloedcellen. Een rode bloedcel leeft gemiddeld drie maanden. Hierdoor geeft de HbA_{1c}-waarde de gemiddelde glucosespiegel in het bloed van de afgelopen drie maanden weer. De behandelend arts probeert met behulp van geneesmiddelen een normale of bijna normale

glucosespiegel te bereiken. De arts wil daarom de HbA_{1c}-waarde onder de 7% (53 mmol/mol) hebben.
De Nederlandse richtlijn voor de behandeling van diabetes adviseert het geneesmiddel metformine als eerste behandeling naast leefstijladviezen, zoals een dieetwijziging, meer lichaamsbeweging en gewichtsverlaging. Als met deze therapieën de bloedglucose nog niet goed genoeg is gedaald, zullen andere geneesmiddelen worden toegevoegd, zoals bijvoorbeeld insuline.
Patiënten met diabetes krijgen vaak hart- en vaatproblemen. Om deze problemen te voorkomen, gebruiken patiënten met diabetes vaak bloeddrukverlagende middelen, cholesterolverlagende middelen (statines) en middelen die de stolling van het bloed remmen (aspirine). In dit proefschrift worden ook deze geneesmiddelen bestudeerd.

Toename van het aantal patiënten met kanker en diabetes
Het aantal mensen dat kanker overleeft is de afgelopen jaren aanzienlijk toegenomen. In 2009 hebben meer dan 400.000 patiënten ooit de diagnose kanker gehad en in 2020 zullen dit meer dan 600.000 patiënten zijn. Deze toename komt gedeeltelijk doordat mensen steeds ouder worden en mensen juist op oudere leeftijd vaker kanker krijgen. Daarnaast zorgt de betere behandeling van kanker ervoor dat minder mensen sterven aan kanker en meer mensen genezen van kanker.
Ook het aantal patiënten met diabetes neemt toe doordat mensen ouder worden en diabetes meestal pas na de leeftijd van 70 jaar ontstaat. Daarnaast heeft de toename van overgewicht en het gebrek aan lichaamsbeweging in de maatschappij hierin ook een belangrijke rol.
Doordat steeds meer mensen ooit één van deze twee ziekten krijgen, zal ook het aantal mensen dat beide ziekten krijgt stijgen. In de afgelopen 15 jaar is in Nederland het aantal kankerpatiënten mét diabetes zelfs al verdubbeld. Dus, artsen zullen steeds meer patiënten op hun spreekuur zien die beide ziekten hebben.

Diabetes en kanker – een gevaarlijke combinatie?
Diabetes en kanker komen veel vaker samen voor dan we op basis van kans zouden verwachten. In 2009 liet een studie zien dat sommige kankersoorten zich vaker ontwikkelen in patiënten met diabetes. Mensen met diabetes krijgen twee keer zo vaak lever-, alvleesklier- of baarmoederkanker dan mensen zonder diabetes. Ook hebben ze meer kans op het krijgen van dikkedarm-, borst- en blaaskanker. Als gevolg hiervan, heeft inmiddels bijna 1 op de 5 kankerpatiënten op het moment van de kankerdiagnose ook al diabetes.
Deze patiënten met diabetes én kanker lijken daarnaast ook vaker te overlijden

dan kankerpatiënten zonder diabetes. Omdat deze patiënten aan beide ziekten kunnen overlijden, is het wel begrijpelijk dat ze vaker overlijden dan patiënten die maar één van de twee ziekten hebben. Maar misschien zorgt de combinatie van beide ziekten ervoor dat patiënten nog vaker overlijden. Dit zou kunnen komen doordat kanker een slechte invloed heeft op diabetes óf diabetes een slechte invloed heeft op kanker. Dus, beïnvloeden deze ziekten elkaar zo, dat er andere (onbekende) factoren nu zorgen voor deze slechtere overleving van patiënten met kanker én diabetes?
Doordat beide ziekten vaak samen voorkomen en doordat patiënten met diabetes én kanker vaker overlijden dan patiënten met één van de twee ziekten, is het van groot belang deze groeiende groep van patiënten te bestuderen.

Doel van dit proefschrift

In dit proefschrift wordt de relatie tussen diabetes, kanker en overleving onderzocht. De belangrijkste doelstellingen van de in dit proefschrift beschreven studies zijn:

- Evalueren van het effect van diabetes op de behandeling van kanker, de terugkeer van kanker en het overlijden aan kanker bij patiënten.
- Bepalen of en hoe het gebruik van de geneesmiddelen: metformine, statines en aspirine, de overleving beïnvloedt van patiënten met dikkedarmkanker én diabetes.
- Bekijken of de bloedglucosewaarden en de therapietrouw van patiënten met diabetes die glucoseverlagende geneesmiddelen gebruiken verandert op het moment van een diagnose kanker.

Onderzoeksgegevens

Om de onderzoeksvragen te beantwoorden heb ik gegevens gebruikt van de Eindhovense kankerregistratie. Voor de meeste studies zijn deze gegevens gekoppeld met de databanken van het PHARMO Instituut. Deze gekoppelde databanken overlappen wat betreft patiënten gedeeltelijk. Samen dekken ze een geografische regio in het Zuidoostelijke deel van Nederland van ongeveer één miljoen inwoners. Gedetailleerde gegevens over een tumor (ernst tumor, soort tumor en kankerbehandeling) van deze patiënten zijn beschikbaar via de kankerregistratie. Gegevens van de geneesmiddelen die zijn opgehaald bij de apotheek, zijn beschikbaar via de PHARMO databanken van zowel de periode voor als na de kankerdiagnose. Van een deel van de patiënten hebben we ook de laboratoriumresultaten voor het onderzoek ter beschikking. Alle studies zijn uitgevoerd bij het Integraal Kankercentrum Nederland (IKNL), locatie Eindhoven, in samenwerking met het PHARMO Instituut in Utrecht en de 10 ziekenhuizen in de regio van het voormalige Integraal Kankercentrum Zuid (IKZ).

Belangrijkste bevindingen van dit proefschrift

Literatuuroverzicht

Dit proefschrift start met een overzichtsartikel waarin we hebben bekeken welke al bekende factoren mogelijk de relatie tussen diabetes, kanker en het hogere risico om te overlijden bij mensen met beide ziekten kunnen verklaren (**Hoofdstuk 2**). In dit artikel vonden we dat de aanwezigheid van bijkomende ziekten en bekende risicofactoren van diabetes én kanker, zoals oudere leeftijd, roken, ongezond eten, overgewicht en onvoldoende lichaamsbeweging, een rol spelen bij de onderzochte relatie. Verder is het belangrijk dat nieuwe studies, die de relatie tussen diabetes, kanker en overleving onderzoeken, rekening houden met de uitgebreidheid van de tumor en de verschillen in de gekregen kankerbehandeling. Ook zullen nieuwe studies zich vooral moeten richten op specifieke problemen na een kankerdiagnose, zoals het risico op terugkeer van kanker en het risico om te overlijden aan de kanker. Dus, het is een grote uitdaging om de relatie tussen diabetes, kanker en overleving geheel te begrijpen. Nieuwe studies moeten rekening houden met heel veel factoren die een rol kunnen spelen in deze relatie.

Invloed diabetes op de kankerbehandeling en overleving van kankerpatiënten

De aanwezigheid van diabetes kan invloed hebben op de tumorkarakteristieken op het moment van de kankerdiagnose, op het krijgen van een kankerbehandeling of op kanker gerelateerde uitkomsten. Wanneer dit zo is, zal diabetes waarschijnlijk een groot effect hebben op de kans om te overleven voor kankerpatiënten. In dit proefschrift werd het effect van diabetes op de uitgebreidheid van de tumor op kankerdiagnose, de kans op terugkeer van kanker en de overleving onderzocht bij patiënten met baarmoederkanker (**Hoofdstuk 3**). Voor het onderzoek werden 1.644 nieuwe patiënten met baarmoederkanker tussen 2000 en 2008 geselecteerd uit de Eindhovense Kankerregistratie. Patiënten met baarmoederkanker én diabetes hadden een minder goede overleving dan patiënten zonder diabetes. Na vijf jaar leefde nog 68% van de patiënten met baarmoederkanker én diabetes en nog 84% van de patiënten met baarmoederkanker zonder diabetes. Diabetes leek invloed te hebben op de tumorkarakteristieken bij de kankerdiagnose. Patiënten met diabetes hadden namelijk vaker een verder gevorderde ziekte dan patiënten zonder diabetes. Nadat we rekening hielden met dit verschil in de uitgebreidheid van kanker in de statistische analyse, hadden patiënten met diabetes ten opzichte van patiënten zonder diabetes, geen grotere kans om te overlijden aan baarmoederkanker zelf. De aanwezigheid van diabetes zorgde ook niet voor een grotere kans op het terugkeren van kanker.

De minder goede overleving in baarmoederkankerpatiënten met diabetes ten opzichte van patiënten zonder diabetes, lijken we dus niet geheel te kunnen

verklaren door een invloed van diabetes op de kanker zelf. Waarschijnlijk overlijden baarmoederkankerpatiënten vaker aan andere oorzaken dan kanker, zoals hart- en vaatziekten of complicaties van diabetes, zoals nierziekten.

Als een kankerpatiënt niet behandeld wordt voor zijn kanker, zal zijn kans op genezing en overleving dalen. We onderzochten in dit proefschrift of patiënten met dikkedarmkanker én diabetes minder vaak werden behandeld voor hun kanker in vergelijking met patiënten zonder diabetes (Hoofdstuk 4). Voor deze studie selecteerden we 11.893 patiënten met dikkedarmkanker en 5.277 patiënten met endeldarmkanker tussen 1995 en 2010 uit de Eindhovense Kankerregistratie. Van de patiënten met dikkedarmkanker had 14% diabetes op het moment van kankerdiagnose en bij de endeldarmkankerpatiënten was dit 12%. Patiënten met dikkedarmkanker (ziektestadium III) én diabetes kregen minder vaak chemotherapie dan patiënten zonder diabetes. Echter bij zowel dikkedarmkankerpatiënten met als zonder diabetes nam het gebruik van chemotherapie sterk toe over de jaren. Endeldarmkankerpatiënten (ziektestadium II/III) kregen over de jaren ook steeds meer bestraling. Het aantal patiënten met en zonder diabetes dat werd bestraald, werd zelfs ongeveer gelijk (81% van de diabeten en 87% van de niet diabeten). Dus, deze studie liet zien dat een steeds groter deel van de patiënten met dikkedarmkanker én diabetes chemotherapie en bestraling krijgen. Echter, patiënten met diabetes krijgen nog steeds minder vaak chemotherapie dan patiënten zonder diabetes. We weten niet of dit betekent dat: 1. De artsen terecht minder vaak chemotherapie geven omdat diabeten een hoger risico op complicaties van chemotherapie hebben. 2. Zij patiënten onterecht te weinig behandelen en daarmee de overlevingskansen van deze patiënten verminderen.

Invloed geneesmiddelen op overleving van patiënten met dikkedarmkanker
In de afgelopen tien jaar is er steeds meer bewijs gekomen dat de relatie tussen diabetes en de kans om te overlijden voor kankerpatiënten afhankelijk is van het glucoseverlagend middel dat gebruikt wordt (metformine of insuline). In dit proefschrift hebben we bekeken of patiënten met dikkedarmkanker die metformine gebruikten na de kankerdiagnose een betere overleving hadden dan degenen die sulfonylureumderivaten gebruikten (Hoofdstuk 5). Met andere woorden: wat heeft elke extra dag inname van metformine (ten opzichte van sulfonylureumderivaten) na dikkedarmkanker voor invloed op de kans om te overleven? In onze statistische analyses zagen we dat het gebruik van metformine (elke extra maand gebruik) na de diagnose dikkedarmkanker geen invloed had op de kans om te overleven. Wel zagen we dat patiënten die metformine gingen gebruiken al een 59% lager risico hadden om te overlijden vóórdat ze het medicijn hadden gebruikt. Dit komt dus niet door het medicijn zelf, maar zeer waarschijnlijk doordat de

patiënten die metformine gebruiken over het algemeen gezonder zijn dan patiënten die sulfonylureumderivaten krijgen. Studies die het effect van metformine op de kans om te overleven voor kankerpatiënten bestuderen, zullen rekening moeten houden met patiëntverschillen tussen de geneesmiddelengroepen. Een arts schrijft bij de ene patiënt metformine voor en bij de andere sulfonylureumderivaten. Heel veel factoren, zoals het gewicht en andere bijkomende ziekten, spelen bij de keuze van de arts een rol. Is de patiënt die metformine gaat krijgen al 'gezonder' voordat deze start met metformine? Gerelateerd hieraan hebben wij een ingezonden brief gestuurd naar aanleiding van een recent gepubliceerde studie. Deze studie keek naar het effect van metformine op de kans om te overleven voor prostaatkankerpatiënten (**Hoofdstuk 6**). In de brief aan het tijdschrift legden wij uit dat de auteurs van het artikel hun conclusie baseerde op een voordeel van metformine wat er al was bij nul dagen gebruik van metformine. Dit kan dus geen effect van metformine zijn, maar eerder een gevolg van patiëntverschillen tussen de geneesmiddelengroepen.

Statines (cholesterolverlagers) en aspirine (antistollingsmiddel) zijn twee geneesmiddelen(groepen) die vaak worden voorgeschreven aan mensen met diabetes. Beide geneesmiddelen hebben mogelijk ook een effect op de kans om te overleven voor kankerpatiënten. Wij hebben onderzocht of het gebruik van metformine, statines en aspirine na een diagnose dikkedarmkanker (onafhankelijk van elkaars gebruik) invloed heeft op de kans om te overleven voor patiënten met diabetes (**Hoofdstuk 7**). De patiënten die wij selecteerden voor de studie hadden al diabetes voordat zij de diagnose kanker kregen. In onze statistische analyses zagen we dat het gebruik van metformine en aspirine (elke extra maand gebruik) na de diagnose dikkedarmkanker geen invloed had op de kans om te overleven. Maar, de overleving van patiënten met dikkedarmkanker én diabetes verbeterde wel duidelijk met elke extra maand van statine gebruik. Onze bevindingen suggereren dus dat statines een gunstig effect hebben op de kans om te overleven voor patiënten met dikkedarmkanker. Omdat we het effect van statines hebben onderzocht in een observationele studie – gegevens zijn verzameld uit de klinische praktijk – worden onze resultaten beïnvloed door de beslissingen die een arts maakt. Artsen kunnen statines juist voorschrijven aan de 'gezondste' patiënten. Maar artsen kunnen de 'ongezondste' patiënten ook adviseren te stoppen met statines. Hierdoor lijken statines een gunstig effect op de prognose te hebben, terwijl het eigenlijk komt doordat alleen de 'gezondste' patiënten statines krijgen voorgeschreven.

Invloed kanker op diabetescontrole en therapietrouw diabeten

De meeste studies die de relatie tussen diabetes, kanker en overleving onderzochten, richtten zich op de invloed van diabetes en glucoseverlagende middelen op kanker. Het omgekeerde effect, de invloed van kanker en de kankerbehandeling op diabetescontrole heeft maar zeer weinig aandacht gekregen. In dit proefschrift hebben we de invloed van kanker en de behandeling hiervan op HbA_{1c}-waarden (maat voor bloedglucose) onderzocht bij patiënten met diabetes die glucoseverlagende middelen gebruikten (**Hoofdstuk 8**). Het HbA_{1c} veranderde rondom de diagnose dikkedarmkanker. De waardes daalden in de twee jaar voorafgaande aan de diagnose kanker voor alle patiënten met dikkedarmkanker. Ze stegen in de twee jaar na de diagnose kanker in patiënten met dikkedarmkanker die niet uitging van de endeldarm (laatste deel dikkedarm). De meest duidelijke verlaging in het HbA_{1c} werd gezien in patiënten met kanker in het eerste deel van de dikkedarm. Maar ook bij mensen die voor de kankerdiagnose geneesmiddelen gebruikten voor een bloedarmoede veroorzaakt door een ijzertekort. Onze resultaten kunnen betekenen dat de diabetescontrole (de bloedglucose) verbetert door kanker. Maar mogelijk ook dat bij patiënten die geneesmiddelen voor een bloedarmoede gebruiken, de HbA_{1c}-waarde geen goede maat is voor de bloedglucose.

De aanwezigheid van kanker kan invloed hebben op de therapietrouw. Het trouw zijn aan glucoseverlagende middelen is cruciaal om een goede diabetesinstelling te bereiken. Daarom is het ook van belang voor de kans om te overleven voor een patiënt. In dit proefschrift hebben we de invloed van kanker (alle soorten) op het trouw zijn aan glucoseverlagende middelen onderzocht bij diabetespatiënten (**Hoofdstuk 9**). Diabetespatiënten die kanker kregen werden vergeleken met diabetespatiënten die geen kanker kregen met eenzelfde duur van diabetes. Om de therapietrouw te bepalen hebben we per maand berekend welk deel van die maand glucoseverlagende middelen werden gebruikt door de patiënt met diabetes. Wanneer de patiënt de helft van de maand glucoseverlagende middelen had gebruikt, hadden we dus een waarde van 50%. In de studie veranderde de therapietrouw op het moment van een kankerdiagnose. De grootste daling in therapietrouw, veroorzaakt door de aanwezigheid van kanker, werd gezien in patiënten met long-, slokdarm-, maag-, dikkedarm-, alvleesklier- en leverkanker. Bij deze patiënten daalde de therapietrouw met 15%. Met andere woorden: door de diagnose kanker gebruikten diabetespatiënten 5 dagen per maand geen glucoseverlagende middelen meer, terwijl ze dat eerst wel deden. Het is niet duidelijk wat deze 5 dagen zonder glucoseverlagend middel voor invloed hebben op de kans om te overleven voor kankerpatiënten. Daarnaast, zal de reden van deze daling in therapietrouw verder onderzocht moeten worden. Komt het doordat

de patiënt het gevecht tegen kanker belangrijker vindt? Adviseert de arts juist om te stoppen met de glucoseverlagende middelen, omdat de bloedglucose verbetert?

Concluderende opmerkingen

Het aantal patiënten met diabetes én kanker neemt sterk toe. In de afgelopen 15 jaar is in Nederland het aantal kankerpatiënten met diabetes zelfs al verdubbeld. Daarom is het van groot belang te begrijpen welke factoren bijdragen aan de hogere kans op overlijden gezien voor kankerpatiënten met diabetes in vergelijking met kankerpatiënten zonder diabetes. Dit proefschrift geeft verdere aanknopingspunten hoe de relatie tussen diabetes en kanker de kans om te overleven voor patiënten beïnvloedt. Zo werd er gezien dat bij patiënten met baarmoederkanker de slechtere overleving van diabetespatiënten waarschijnlijk niet werd veroorzaakt door een effect van diabetes op de kanker zelf. Waarschijnlijk zullen andere ziekten de overleving van deze patiënten beïnvloeden. Artsen zullen moeten worden aangemoedigd om bij patiënten met baarmoederkanker én diabetes, aandacht te besteden aan de diabetesinstelling om zo diabetescomplicaties te voorkomen. Daarnaast laat dit proefschrift zien dat diabetes invloed heeft op het aantal patiënten dat voor hun dikkedarmkanker een kankerbehandeling krijgt. Dit zal mogelijk de kans op genezing en dus ook de kans om kanker te overleven beïnvloeden. Onze en andere studies suggereren momenteel steeds meer dat er geen relatie bestaat tussen het gebruik van metformine en de kans om te overleven voor patiënten met dikkedarmkanker. Echter, het gebruik van statines lijkt de kans om te overleven na de diagnose dikkedarmkanker te verbeteren en lijkt dus veelbelovend. Dit zal prioriteit moeten hebben op onderzoeksagenda's. Verder toont dit proefschrift aan dat de bloedglucose bij diabetespatiënten waarschijnlijk verbeterde door een diagnose dikkedarmkanker. Maar we zagen ook dat het trouw zijn aan glucoseverlagende middelen bij diabeten verslechterde rondom de kankerdiagnose. Dit kan betekenen dat de arts op basis van een verbeterde bloedglucose adviseert te stoppen met de glucoseverlagende middelen. Ook kan het betekenen dat de patiënt het gevecht tegen kanker belangrijker vindt dan het adequaat slikken van zijn geneesmiddelen voor de behandeling van diabetes. Voor de huidige medische praktijk met patiënten met kanker én diabetes, dragen de resultaten van dit proefschrift bij aan de bewustwording van de gevaarlijke 'liaison' tussen diabetes en kanker, met al zijn facetten.

List of publications

Publications included in this thesis:

1. Zanders MMJ, Vissers PAJ, Haak HR, van de Poll-Franse LV. Colorectal cancer, diabetes and survival: epidemiological insights. *Diabetes & Metabolism, 2014, 40(2):120-127*.

2. Zanders MMJ, Boll D, van Steenbergen LN, van de Poll-Franse LV, Haak HR. Effect of diabetes on endometrial cancer recurrence and survival. *Maturitas, 2013, 74(1):37-43*.

3. Zanders MMJ, van Steenbergen LN, Haak HR, Rutten HJT, Pruijt JFM, Poortmans PMP, Lemmens VEPP, van de Poll-Franse LV. Diminishing differences in treatment between colorectal cancer patients with and without diabetes: a population-based study. *Diabetic Medicine, 2013, 30(10):1181-1188*.

4. Zanders MMJ, Vissers PAJ, van Herk-Sukel MPP, Ruiter R, Hollestein LM, Haak HR, Herings RMC, Stricker BHCh, Lemmens VEPP, van de Poll-Franse LV. Exposure to metformin started after colorectal cancer diagnosis and mortality: using a novel approach with time-varying exposure. *Submitted*.

5. Zanders MMJ, Vissers PAJ, van de Poll-Franse LV. Association between metformin use and mortality in prostate cancer patients – explained by confounding by indication? *Journal of Clinical Oncology, 2014, 32(7):701*.

6. Zanders MMJ, van Herk-Sukel MPP, Vissers PAJ, Herings RMC, Haak HR, van de Poll-Franse LV. Is there still an effect of metformin, statin and aspirin use on overall mortality among colorectal cancer patients with diabetes if adjusted for one another? *Submitted*.

7. Zanders MMJ, van Herk-Sukel MPP, Herings RMC, van de Poll-Franse LV, Haak HR. Impact of cancer diagnosis and treatment on glycaemic control among individuals with colorectal cancer using glucose lowering drugs. *Submitted*.

8. Zanders MMJ, Haak HR, van Herk-Sukel MPP, van de Poll-Franse LV, Johnson JA. Impact of cancer on adherence to glucose lowering drugs in individuals with diabetes. *Submitted*.

Other publications:

1. Vissers PAJ, Zanders MMJ, Voogd AC, van Herk-Sukel MPP, Ruiter R, Hollestein LM, Herings RMC, Stricker BHCh, van de Poll-Franse LV. The effect of starting metformin in comparison with sulfonylurea derivatives after breast cancer diagnosis on overall mortality. *Submitted*.

2. Voorneveld PW, Reimers MS, Bastiaannet E, Jacobs RJ, van Eijck R, Zanders MMJ, Herings RMC, van Herk-Sukel MPP, Kodach LL, van Wezel T, Kuppen PJK, Morreau H, van de Velde CJH, Hardwick JCH, Liefers GJ. Statin use after diagnosis improves survival in colorectal cancer patients. *Submitted*.

3. De Bruijn, KMJ, Hansen BE, Zanders MMJ, van Herk-Sukel MPP, van de Poll-Franse LV, van Eijck CHJ. Diabetes mellitus tends to decrease chances of surgery in patients with esophageal adenocarcinoma. *Submitted*.

4. Zanders MMJ, Vissers PAJ, van de Poll-Franse LV. Effect of metformin on survival of colorectal cancer patients in daily practice [Effect van metformine op de overleving van patiënten met een colorectaal carcinoom in de dagelijkse praktijk]. *Submitted*.

5. Zanders MMJ, Renehan AG, Bowker SL, Carstensen B, van de Poll-Franse, Johnson JA. Comment on Bordeleau et al. The Association of Basal Insulin Glargine and/or n-3 Fatty Acids With Incident Cancers in Patients With Dysglycemia. Diabetes Care 2014;37:1360-1366. *Diabetes Care, 2014, 37(10):e221-222*.

6. Vissers PAJ, Thong MSY, Pouwer F, Zanders MMJ, Coebergh JWW, van de Poll-Franse LV. The impact of comorbidity on Health-Related Quality of Life among cancer survivors: analyses of data from the PROFILES registry. *Journal of Cancer Survivorship, 2013, 7(4):602-613*.

7. Zanders MMJ, van de Poll-Franse LV. Diabetes and Cancer: increasing demand for multidisciplinary action [Diabetes en kanker: toenemende vraag naar multidisciplinair handelen]. *Modern Medicine, 2011, 35(11): 369-371*.

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Marjolein

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About the author

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Marjolein M.J. Zanders was born on the 23th of September 1987 in Weert, the Netherlands. She finished secondary education at the Philips van Horne SG in Weert in 2005 and subsequently started medical school at Maastricht University. After receiving her Bachelor's degree in Medicine in 2008 and finishing her regular internships, she conducted her scientific internship. This internship focused on 'Endometrial cancer, diabetes and survival', under supervision of prof. dr. H.R. Haak (Internal medicine, Máxima Medical Centre) and prof. dr. L.V. van de Poll-Franse (Research, Netherlands Comprehensive Cancer Organisation). In 2011 she received her Master's degree in Medicine. Subsequently, she started her PhD project at the Netherlands Comprehensive Cancer Organisation, location Eindhoven, on the subject of 'Diabetes, cancer and survival'. As part of her PhD training she joined the ACHORD Research group at the University of Alberta in Edmonton, Canada, for three months (supervisor: prof. dr. J.A. Johnson). During her PhD training she followed several epidemiological courses and she will gain her registration as an Epidemiologist in 2015. In April 2015 she will start her residency in Internal Medicine at the 'Máxima Medical Centre' in Eindhoven/ Veldhoven (head: dr. A.G. Lieverse) as part of her specialty training at Maastricht University Medical Centre+ (head: prof. dr. C.D.A. Stehouwer).